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PRELIMINARY ANALYSIS OF FUNCTIONS OF THE TEMPORAL LOBES IN MONKEYS

HEINRICH KLÜVER, PH.D.

AND

PAUL C. BUCY, M.D.

CHICAGO

In previous communications [1] we pointed out that the chief symptoms following bilateral temporal lobectomy in the rhesus monkey consist in "psychic blindness" (*Seelenblindheit*) or visual agnosia, strong "oral" tendencies and profound emotional changes. Our results were primarily based on an analysis of the behavioral symptoms of a female rhesus monkey which had been studied for a period of four months following the operations. The type of disturbance analyzed in that case seemed to be similar to the "associative mind blindness" of Lissauer.[2] It is true that the diagnosis "agnosia" can be only of practical importance and merely serves to raise a number of questions. A review of the clinical literature indicates that the more carefully a case is studied the more difficult it may be to decide whether there is really an "agnostic" or merely a "visual" defect, that is, whether the variety of "agnostic" symptoms can be reduced to disturbances of "elementary" or "higher" visual functions. Von Monakow [3] and Mourgue [4] even

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From the Otho S. A. Sprague Memorial Institute and the Division of Neurology and Neurosurgery, University of Chicago.

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1. Klüver, H., and Bucy, P. C.: (*a*) "Psychic Blindness" and Other Symptoms Following Bilateral Temporal Lobectomy in Rhesus Monkeys, Am. J. Physiol. **119**:352-353, 1937; (*b*) An Analysis of Certain Effects of Bilateral Temporal Lobectomy in the Rhesus Monkey, with Special Reference to "Psychic Blindness," J. Psychol. **5**:33-54, 1938.

2. Lissauer, H.: Ein Fall von Seelenblindheit nebst einem Beitrage zur Theorie derselben, Arch. f. Psychiat. **21**:222-270, 1890.

3. von Monakow, C.: Die Lokalisation im Grosshirn und der Abbau der Funktionen durch kortikale Herde, Wiesbaden, J. F. Bergmann, 1914.

4. Mourgue, R.: Neurobiologie de l'hallucination: Essai sur une variété particulière de désintégration de la fonction, Bruxelles, Maurice Lamertin, 1932.

raised the question whether the disturbances in the process of recognition commonly referred to as "agnosia" are the result of an emotional indifference of the subjects, or, in other words, whether "agnostic" symptoms represent merely disturbances in the affective sphere. In view of this situation, we can consider the "psychic blindness" and related symptoms, as described in our first report, merely the starting point for further analysis. It seemed desirable to produce, if possible, the same symptoms in a larger number of cases and to extend the behavioral analysis in certain directions in order to gain a better understanding of the nature of the disturbance following removal of both temporal lobes.

TESTING PROCEDURES

In addition to general observations on locomotion, drinking, eating, sleeping and other forms of activity displayed by the animals while kept in cages, we made use of a variety of special tests. Most of these procedures represent methods or modifications of methods previously devised by one of us for analyzing the behavior of subhuman primates.[5] With the exception of our first monkey,[1b] which was observed previous to the operations only generally, all animals were tested before and after operation. In case the operation was performed in two or more stages, the animal was also subjected to interoperative tests. In the following sections, we shall briefly indicate the procedures and test situations employed. A detailed description of the tests will be published later.

1. *Investigation of Sensory and Motor Factors.*—In addition to utilizing conditioned differential reactions as indicators (see "Differential Reactions"), we recorded the reactions of the animal to various stimuli and test situations. Although in most instances quantitative data were not obtained, the tests were designed to enable us to determine at least the presence of gross sensory and motor defects. The procedures used have been briefly described in our first report.[1b] The investigation of visual reactions was confined to the following items: visual reflexes; the ability to appreciate differences in brightness, size, shape, distance or position of objects; and visual field defects. For example, in obtaining data on visual acuity we utilized pulling-in reactions; the caged-in animal was required to pull in black or white threads a fraction of a millimeter in diameter and lying on a black or white ground or on surfaces exhibiting complex visual patterns. In determining visual field defects, various methods of "food perimetry" and the "hemianopic testing board" [5c] were used. The application of the pulling-in technic [5a] made it possible to obtain data on the speed of motor reactions, handedness and various motor habits.

2. *Determination of Lateral Tendencies.*—Two or more similar objects were placed before the experimental cage. In reacting to objects in a row, any monkey may display strong right or left tendencies; that is, it may tend to pick up or pull in such objects as pieces of food, strings or boxes from the right to the left or

5. Klüver, H.: (*a*) Behavior Mechanisms in Monkeys, Chicago, University of Chicago Press, 1933; (*b*) An Auto-Multi-Stimulation Reaction Board for Use with Sub-Human Primates, J. Psychol. **1**:123-127, 1935; (*c*) Certain Effects of Lesions of the Occipital Lobes in Monkeys, ibid. **4**:383-401, 1937.

vice versa. The test situations employed have been extensively used in a previous study of hemianopic monkeys.[6]

3. *Multiple Object Tests.*—Different objects were placed in a row on a table on a piece of cardboard or were suspended from a horizontal string running parallel with the front of the cage and then brought within reach of the animal. In some tests the animal could view the objects before they were placed within reach; in others they were kept out of view until presented. The rows of objects contained either one or more pieces of food or none at all. The objects presented included such items as objects made of glass, wood, paper or metal; feces; live animals; toys; spots of moisture, and drawings made with ink or chalk. In most tests each object was different, but in some tests two or more of the inedible objects were alike.

4. *Investigation of Reactions When Monkey was Free in Room.*—The animal was turned loose in a large room which contained pieces of apparatus and furniture, and on the floor of which had been placed various objects, including several pieces of food. During a thirty minute period the reactions were observed by the experimenter and an assistant, who sat in different corners of the room.

5. *"Concentration" Test.*—The apparatus, previously described,[7] consists essentially of a rotating platform on which the center of a board, 180 cm. long and 3.5 cm. wide, is fastened. The positions of the apparatus and the experimental cage were so adjusted that the monkey was able to reach one end of the rotating board for a short time every thirty seconds. A piece of food was placed on one end of the board and a nail or metal nut on the other. The animal could, therefore, obtain one edible and one inedible object per minute.

6. *Pulling-in Tests.*—The tests either represented "string experiments"[5a] or required the pulling in of a box under different conditions. One, several or all of the strings lying within easy reach of the monkey were baited with food or some inedible object. Different "string configurations" were obtained by varying the number, position, length, direction and distance of the strings from each other.

7. *Differential Reactions Established by Training.*—The technics used, which have been previously described, included: (*a*) the "form board," for establishing reactions to visual differences;[8] (*b*) the "automultistimulation reaction board," with two plates for establishing reactions to differences in sound,[5b] and (*c*) the pulling-in technic, with movable stimulus boxes for establishing reactions to differences in weight.[5a] It should be remarked that "form boards" with one as well as with two holes were used. In tests with the one hole "form board" the animal simply had to push aside the stimulus object, for instance, a circle, to gain access to the food. Differential reactions were established only in 4 of the 8 animals with bilateral temporal lobectomy and in monkey 16 (see "Subjects"). This was done partly in view of Munk's results with dogs. It was thought desirable to have available a series of animals which had not been subjected to systematic training procedures. Monkeys 1, 5 and 6 were trained to respond positively to a circle and negatively to a square of the same size. In critical trials following the training, groups of equivalent and nonequivalent stimuli were determined. Monkey 8 was trained to react negatively to a sound, the sound being produced by a Cenco impulse counter, and positively to "silence." Monkey

6. Klüver,[5c] pp. 386 and 387.

7. Klüver and Bucy.[1b] Klüver.[5a]

8. Klüver.[5c] Klüver and Bucy.[1b]

6 was trained to react positively to the lighter of two weights in the 1,050 and 350 Gm. pair. Finally, monkey 16 was trained to respond positively to a circle instead of a square and to respond positively to a 1,150 instead of a 350 Gm. weight.

8. *Investigation of Reactions in the Presence of Animate and Inanimate Objects.*—The response of the animal to the presentation of single objects likely to elicit characteristic forms of behavior, especially emotional reactions, was studied. We employed such objects as a snake, a cat, a dog, a rat, a mirror, a metal stick (such as is used in transferring a monkey from one cage to the other) and a catcher (used in catching monkeys).

9. *Investigation of Implement-Using Behavior.*—Analysis of the ability to utilize objects as "tools," as previous studies have indicated,[9] seems worth while only in the case of Cebus monkeys. The present series includes 1 Cebus monkey (case 5); all the other animals were macaques. Implement-using behavior was studied only in the case of the Cebus monkey.

SURGICAL PROCEDURES

We shall briefly indicate the procedures employed in temporal lobectomy. In all cases anesthesia was induced by intraperitoneal injection of pentobarbital sodium. A temporal osteoplastic flap was reflected downward from over the temporal lobe. The pia-arachnoid membrane was coagulated and then cut with the Bovie high frequency current just below and parallel to the sylvian vessels and transversely across the temporal lobe at the level of the anastomotic vein of Labbé, if it occupied its usual position, or at a point just posterior to the lower end of the central sulcus. A blunt spatula was then inserted along these lines of incision and the lobe, including its medial surface, removed. Bleeding was controlled with the Bovie cautery. Whenever possible, the tissue was removed in a single block, weighed and preserved for histologic examination. The wound was carefully dried and the bone flap replaced. Muscle and scalp were closed with several layers of silk sutures.

Some of the animals have been killed, while others are still being studied. The brains of the animals killed have been or are being serially sectioned, and the sections have been stained both for myelinated fibers (by Weil's method) and for cellular elements (with cresyl violet).

A preliminary microscopic examination, for instance, of the brain of monkey 4 has shown that the extirpation included Brodmann's areas 22, 21 and 20, with the exception of the upper part of area 22 lying anterior to area 19. The uncus and almost the entire hippocampus were removed. Throughout the extent of the lesion only a thin dorsomedial strip of the hippocampus remained. Posteriorly, as the hippocampus turns dorsally toward the hippocampal commissure, about one fifth of this structure remained. The basal ganglia were not damaged except for the amygdala, which had been largely removed, and the tail of the caudate nucleus, which had been removed or seriously damaged.

SUBJECTS

In the following list we have indicated the species, the sex and weight of the animal, the type and date of the operation and the date of death, if it has

9. Klüver, H.: Re-Examination of Implement-Using Behavior in a Cebus Monkey After an Interval of Three Years, Acta psychol. **2**:347-397, 1937; footnote 5a.

occurred. In 7 of the 8 cases of bilateral temporal lobectomy the operation was performed in two stages. In 1 case both lobes were removed simultaneously (case 8). Cases 9 to 15 represent animals in which the temporal lobes were severed from either the frontal or the occipital lobes or in which one or portions of one or of both temporal lobes were removed. In case 16 one temporal lobe was extirpated subsequent to removal of both prefrontal areas.

CASE 1.—A female rhesus monkey (Macaca mulatta), weighing 6.3 Kg., underwent extirpation of the left temporal lobe on Dec. 7, 1936 and extirpation of the right temporal lobe on Jan. 25, 1937. The animal was killed on Dec. 7, 1938.

CASE 2.—A male rhesus monkey, weighing 3.8 Kg., underwent extirpation of the left temporal lobe, on Feb. 1, 1937 and extirpation of the right temporal lobe on Feb. 23, 1937. The animal was killed on July 8, 1937.

CASE 3.—A male rhesus monkey, weighing 3.42 Kg., underwent extirpation of the right temporal lobe on Feb. 4, 1937 and extirpation of the left temporal lobe on Sept. 17, 1937. The animal was killed on Oct. 27, 1937.

CASE 4.—A female rhesus monkey, weighing 3.36 Kg., underwent extirpation of the right temporal lobe on Feb. 11, 1937 and extirpation of the left temporal lobe on February 23, 1937. The animal was killed on March 18, 1937.

CASE 5.—A male Cebus monkey (Cebus capucina), weighing 2.82 Kg., underwent extirpation of the left temporal lobe on Sept. 17, 1937 and extirpation of the right temporal lobe on Oct. 15, 1937. The animal is still living.

CASE 6.—In a male rhesus monkey, weighing 2.72 Kg., the olfactory tracts were cut on July 22, 1938. The right temporal lobe was extirpated on Nov. 25, 1938 and the left temporal lobe on Jan. 27, 1939. The animal is still living.

CASE 7.—In a male rhesus monkey, weighing 4.65 Kg., the left temporal lobe was extirpated on Dec. 20, 1938 and the right temporal lobe on Feb. 6, 1939. The animal is still living.

CASE 8.—A male rhesus monkey, weighing 4.9 Kg., underwent simultaneous bilateral extirpation of the temporal lobes on Jan. 23, 1939. The animal is still living.

CASE 9.—A male rhesus monkey, weighing 4.04 Kg., underwent extirpation of the first convolution of the left temporal lobe on April 14, 1938 and extirpation of the first convolution of the right temporal lobe on July 8, 1938. The animal is still living.

CASE 10.—A female rhesus monkey, weighing 3.17 Kg., underwent extirpation of the second and third convolutions of the right temporal lobe on May 26, 1938 and extirpation of the second and third convolutions of the left temporal lobe on July 16, 1938. The animal is still living.

CASE 11.—In a female Java monkey, weighing 1.4 Kg., the connections between the temporal and the frontal lobe were severed, i. e., the anterosuperior margin of the lesion produced by temporal lobectomy was duplicated, on the left side on April 18, 1938. Connections between the temporal and the frontal lobe on the right side were severed on July 19, 1938. The animal is still living.

CASE 12.—In a male rhesus monkey, weighing 3.07 Kg., the connections between the temporal and the frontal lobe were severed on the left side on July 12, 1938 and on the right side on Sept. 27, 1938. The animal is still living.

CASE 13.—In a male rhesus monkey, weighing 3.2 Kg., the connections between the temporal and the occipital lobe were severed, i. e., the posterior margin of the lesion produced by temporal lobectomy was duplicated, on the right side on

July 13, 1938. The connections between the temporal and the occipital lobe on the left side were severed on Sept. 29, 1938. The animal is still living.

CASE 14.—A female rhesus monkey, weighing 4.36 Kg., underwent extirpation of the left temporal lobe on Feb. 4, 1937 and was killed on May 17, 1937.

CASE 15.—A male rhesus monkey, weighing 4.2 Kg., underwent extirpation of the second and third convolutions of the left temporal lobe on April 15, 1938. The animal was killed on April 23, 1938.

CASE 16.—A female rhesus monkey, weighing 4.22 Kg., underwent extirpation of the left prefrontal area on Feb. 11, 1937, of the right prefrontal area on May 12, 1938 and of the left temporal lobe on Jan. 30, 1939. The animal is still living.

EFFECTS OF BILATERAL TEMPORAL LOBECTOMY

We shall describe the polysymptomatic picture as observed in the "bilateral temporal" monkey. It should be said first that the present investigation has essentially confirmed the results [1b] obtained in case 1. Such symptoms as were exhibited in case 1 can be observed immediately after extirpation of the second temporal lobe or after simultaneous removal of the two lobes, and although certain changes occur in the course of time, it is worthy of note that the picture found in case 1 about two years after the operations is in most of its characteristic features essentially the same as can be observed in the bilateral temporal monkey as early as twenty-four hours after the operations. We shall first describe forms of behavior which seem to indicate that the ability to recognize and detect the meaning of objects on the basis of visual criteria alone is either lost or seriously disturbed, although the animal exhibits no, or at least no gross, defect in the ability to discriminate visually. We have summarized this group of symptoms under the term "psychic blindness."

"Psychic Blindness."—The bilateral temporal monkey shows a strong tendency to approach animate and inanimate objects without hesitation. This tendency appears even in the presence of objects which previously called forth avoidance reactions, extreme excitement and other forms of emotional response. The animal tends to contact every object in sight and to examine it by mouth rather than by hand. In multiple object tests, the caged-in monkey, even when hungry, will pick up objects indiscriminately either one after the other or, by using both hands, two at a time. After an oral examination, the object, if inedible, such as a nail, a glass, a live mouse, feces or a piece of sealing wax, is discarded, but if edible is immediately consumed. In general, all available objects are examined, even though the first object examined may be the only piece of food present among the objects presented and even though the row of objects lying before the cage may contain no food at all. In a given test situation, an inedible object which has been discarded after a first examination may be reexamined several times. If the row of objects contains, let us say, one piece of food and four inedible objects, the reexamination of such an object as an electric bulb or a socket may take place before or after the food has been picked up. If the same objects are presented again in the next test or on succeeding days the animal examines them as if they were being presented for the first time. In such a

way, a given object may be examined again and again in the course of several months as if it had never been responded to before. The animal tends to examine all available objects, even if two or more of the objects lying in a row are alike. If the inedible objects are not removed after each test, the animal may frequently reexamine them not only between tests but also while a new series of objects is lying before the cage.

Although it has been our endeavor to present as great a variety of objects as possible in the various multiple object situations, we have not succeeded in finding any object which the bilateral temporal monkey did not want to examine. Objects are examined, no matter whether they are very large or very small, dead or alive, edible or inedible, moving or stationary, silent or noisy, solid or figures printed on paper. The monkey seems to be just as eager to examine the tongue of a hissing snake, the mouth of a cat, feces, a wire cage or a wagon as a piece of food.

The tendency to respond indiscriminately to various objects not only appears in the multiple object tests but may be just as strong when the animal is left to itself in its home cage or when it is turned loose in a room. When in its home cage the animal may examine at random pieces of food, the food pan itself, stones, cigaret stubs and wires lying among the pieces of food, the head of a screw in the wall of the cage and a chain hanging down from the door. If free in a large room the animal may contact and examine more than 100 objects in thirty minutes and may pass the pieces of food lying on the floor many times before picking them up. The examination includes such heterogeneous objects as a steel nut in a motor, an iron pipe, the tail of a monkey, a windowpane, the fingers, shoes and stopwatch of the experimenter and a piece of soap. When free in a room, the monkey again tends to reexamine most objects at intervals, so that a given object, let us say an iron pipe, may be examined a dozen times in the course of half an hour. It is worthy of note that the monkey never changes the position of any of the objects in the room and that even very small objects are not carried around. Occasionally an object may be picked up for examination, but then is dropped at the same place. The animal in moving about behaves as if all available objects belonged to one general class, as if they were merely "something to be approached and examined."

In the "concentration" test, in which a piece of food or a metal object passes the experimental cage every thirty seconds, the monkey picks up both the food and the metal object until it ceases reacting to both. The food is eaten, whereas the nail or the steel nut is discarded after an examination by mouth. In some experimental periods, both the food and the inedible object are picked up in 100 per cent of the trials. Even after as many as 260 successive trials the monkey may remove the nail each time it passes, so that finally more than a hundred nails may lie on the floor of its cage. As a rule, however, the monkey is not content with removing and examining the metal object in all, or practically all, trials; it will frequently pick up a nail or a steel nut from the floor of the cage in the intervals between removing an object every thirty seconds. It should be pointed out that the normal monkey in this test situation will let the nail pass by in all trials or pick it up only the first few times.

In pulling-in tests, the animal tends to pull in the strings indiscriminately, no matter whether edible or inedible objects or no objects are attached to them. In fact, the monkey may first examine the cardboard on which the strings are lying, then one string after the other and, finally, after the pulling-in, the object fastened to the string. Again, the strings and objects already pulled in may be

examined between trials. When pulling in boxes, the monkey may examine the string repeatedly during the pulling-in and the box itself before reaching into it.

Oral Tendencies.—There exists a strong tendency to examine all objects by mouth. The fact that in the multiple object tests and in other test situations we have not discovered any kind of object the monkey did not want to examine means, therefore, that we have found no object the animal was not prone to examine orally. This oral examination consists in putting the object into the mouth, biting gently, chewing, licking, touching with the lips and "smelling" by holding the object before the nostrils. At times the object is first put into the mouth and then "smelled"; sometimes the "smelling" occurs first. Either reaction is rarely absent in examining an object. Oral tendencies are present not only in the sense that the animal examines the object orally but also in that it tends to contact the object directly by mouth instead of using its hands. Even in the multiple object tests, in which the objects are lying before the cage, the animal may often attempt to press its head through the bars to establish direct contact with its mouth. Since this is not possible, the monkey is forced to pick up the objects for oral examination. "Objects" which cannot be picked up, such as spots of moisture, drawings made on the table or designs on wallpaper, are frequently touched, rubbed or scratched after futile attempts have been made to pick them up. Such reactions are frequently followed by holding the hand or one finger before the nostrils. The "smelling" of fingers is also observed if an object is beyond reach so that no contact can be established by hand or mouth. Occasionally this "smelling" even precedes the touching or picking up of an object within reach. The monkey may repeatedly stick out its tongue to contact a metal object moving back and forth before the cage, although such an object can be easily reached by hand. The tendency to examine objects orally is not interfered with, of course, when the animal is turned loose in a room. The monkey will run from one object to another and contact and examine the various objects, or parts of them, by mouth. At times the reaction seems to be confined merely to "smelling" glass, metal or other objects, since the mouth does not come in direct contact with the object. When transferred to another cage, the monkey frequently first makes an oral examination of the door, chain, galvanized iron of the floor, heads of nails or other parts of the cage. In the "concentration" test, the hundredth nail picked up is examined orally in the same way as was the first nail removed from the board. In pulling-in tests the monkey examines not only the various objects pulled in but also the stick or the hand of the experimenter used for removing these objects from the experimental cage after completion of the test.

The tendency to examine objects orally is present even though the objects may have acquired "meaning" through previous training. For instance, in the "form board" test the animal is required to choose a circle instead of a square. For the normal monkey which has learned this problem the circle merely points to, or signifies, the presence of food. It is not reacted to for its own sake. It is an object to be pushed aside to gain access to the piece of food. For the bilateral temporal monkey the circle does not signify another object, that is, food, but both circle and square are treated as any other object, that is, as something to be examined. At times both stimulus figures are picked up, examined by mouth and discarded before even an attempt is made to take the piece of food lying in one of the holes. When the automultistimulation reaction board is placed before the cage, the animal may try to contact the apparatus by mouth and, since this is impossible, may at least remove the brass squares, take them into the cage and examine them orally.

It is of great interest that the normal rhesus monkey which gets hold of an inedible object is generally dominated by the tendency to tear it rapidly to pieces by using the hands and mouth. In contrast to this, the bilateral temporal monkey when confronted with a variety of objects evidences a certain lack of aggressiveness toward the objects in the sense that it confines its activities to biting them gently, to licking or to touching them with the mouth; in brief, to examining them orally in different ways. The same type of reaction or, differently expressed, the same lack of aggressiveness toward objects appears when the animal is turned loose in a room. No attempt is made to destroy, break or carry objects around.

The reactions, and especially the oral tendencies, observed in case 6 deserve special comment, as the olfactory tracts of this monkey were cut previous to removing both temporal lobes. After the olfactory tracts were severed, the characteristic gesture of "smelling" an object by holding it before the nostrils was still observed for a week. Thereafter, up to the present, for about ten months, the "smelling," even of pieces of food, has never been observed. After section of the olfactory tracts but prior to removal of the temporal lobes the monkey did not show any tendency to pick up inedible objects; even edible objects, in case the animal was not familiar with them, were frequently not taken. This type of behavior did not change when, after about four months, the right temporal lobe was removed. When the left temporal lobe was extirpated about six months after the olfactory tracts were severed, all of the symptoms characteristic of the bilateral temporal monkey appeared except that no "smelling" was ever observed. Although one of the components in the picture of oral tendencies was absent, it is significant that oral tendencies were present as in any other animal with bilateral temporal lobectomy. The results may be best illustrated by reference to the "concentration" test. After the cutting of the olfactory tracts, the animal picked up the piece of food in 100 per cent and the metal object in 2 per cent of the trials. There was never any "smelling" of the objects. After removal of the right temporal lobe exactly the same results were obtained. When the left temporal lobe was also removed the "smelling" reactions continued to be absent, but the animal now picked up the nail or the steel nut in 92 per cent of the trials and in each case examined the object by mouth before discarding it. In brief, it may be said that the reactions observed in the "concentration" test, the multiple object tests, the pulling-in tests and the other test situations clearly indicated that monkey 6 was not different from any other animal with bilateral temporal lobectomy in its tendency to pick up objects indiscriminately and then examine them by mouth.

"Hypermetamorphosis."—Any description of the typical behavior of the bilateral temporal monkey is incomplete without reference to another characteristic reaction tendency. When the reactions of the monkey to animate and inanimate objects are observed, it frequently appears to the observer as if the animal were acting under the influence of some "compulsory" or "irresistible" impulse. It behaves as if it were "forced" to react to objects, events and changes in the environmental stimulus constellation. Thus, it may be said that in the bilateral temporal monkey there exists an excessive tendency to take notice of and to attend and react to every visual stimulus. The symptom described here has been given various names by neurologists and psychiatrists, for instance, by Wernicke, Sommer, Leupoldt, Steiner and others. For the sake of brevity, we shall adopt the terminology of Wernicke,[10] who spoke of a "hypermetamorphosis" and a "hypermetamorphic impulse to action."

10. Wernicke, C.: Grundriss der Psychiatrie, Leipzig, Georg Thieme, 1906.

The monkey immediately attends to and takes in quickly the various details of a visual situation. The close visual inspection is not confined to objects within reach. The objects singled out for inspection may include such items as an eyelet in a board, a speck of dirt on a mirror, a scratch on the table, a nut in a motor, a stone in a ring, the foot of a toy monkey, a whiff of smoke, cuff buttons, a wrist watch and the mouth of the experimenter. When confronted with a series of objects, the monkey frequently looks from one object to the other before seizing one and often picks up two at a time. In the "concentration" test the animal may almost constantly attend to the end of a moving board and in such a way succeed in removing an object every thirty seconds for more than two hours. It seems clear, therefore, that a "paresis of attention" or similar defects cannot be assumed to account for the picture of "psychic blindness."

The outstanding characteristic of the various reactions is not that the monkey attends visually to such a variety of stimuli and evinces such great curiosity in all kinds of objects and events. The most impressive feature is that the presentation of any visual object will, whenever possible, immediately lead to a motor response. For the bilateral temporal monkey the most heterogeneous objects, varying from a dot in a necktie to the tongue of a hissing snake, have become equivalent in the sense that they evoke the same typical forms of motor behavior. Expressed differently, certain properties of the objects, their being "dangerous," "inedible" or "indifferent," have suddenly become ineffective in determining visually guided reactions. The monkey seems to be dominated by only one tendency, namely, the tendency to contact every object as quickly as possible. The speed with which contact is established is especially great when only a single object is presented. Noticing an object and performing the requisite motor response for contact seem to be a continuous process. When turned loose in a room, the monkey often behaves as if it were ceaselessly "pulled" from one object to another. When the experimenter or a stranger enters the laboratory, the animal may be seen standing in its cage as near to the door as possible and with an arm extended in the direction of the person entering. If the monkey is prevented from establishing contact with an object by the experimenter keeping the object out of reach, it may start examining the objects available in its cage.

The "hypermetamorphic impulse to action" is set off by almost any kind of object. It seems, therefore, that the fact of an object being an object, that is, a "segregated whole," a "discrete something" different from its surroundings, is in itself sufficient for eliciting this impulse. The multiple object tests and other tests demonstrate the strong tendency of the animal to respond to every available object, no matter what its character, and to reexamine it whenever it is noticed again. Whether or not an object is noticed, however, seems to depend on various factors. For instance, every attempt to remove one of the discarded objects from the cage may be immediately followed by grabbing and examining this or some other object or the hand of the experimenter. The monkey, which picks up, let us say, a nail for the hundredth time to examine it, is examining the same object, i. e., a nail, but the very fact that something is presented within reach, either by the experimenter or by an apparatus, makes possible what was impossible a few seconds ago, namely, a transformation of the "hypermetamorphic impulse to action" into action. At any rate, on appearance of the nail the monkey responds by picking it up.

Sensory and Motor Factors.—The question may be raised whether the picture of "psychic blindness," oral tendencies and "hypermetamorphosis" results from a combination of various sensory and motor defects. It appears that defects in

"elementary" sensory functions either do not exist or are of a kind not apt to account for the typical behavior of the monkey.

In cases of visual agnosia the attempt must be made to determine whether visual defects of various kinds can in some way account for the reactions observed. One of us [5c] has shown that visual field defects alone, even if they should exist, cannot be considered sufficient to produce the picture of "psychic blindness." It was found that the various differential responses to visual stimuli established by training were not lost, or were only slightly disturbed, after unilateral occipital lobectomy or bilateral destruction of the macular cortex. In these cases Brodmann's areas 18 and 19 were also injured. Since in these cases even very extensive damage to the visual system did not lead to inability to recognize objects visually, it is difficult to understand why such a defect should appear as a consequence of much smaller field defects, as found in some of our bilateral temporal animals. In some cases of temporal lobectomy no field defects can be demonstrated. Yet the previously described symptoms following bilateral temporal lobectomy are the same in animals with and in those without visual field defects. In case 7 the tests indicate the existence of right homonymous hemianopia. The ability to appreciate differences in brightness, size, shape, distance, position and movement is as little impaired in this monkey as it is in monkeys with the left occipital lobe removed.

Our previous analysis of case 1 made the existence of defects in the upper quadrants highly probable.[1b] Since then, the existence of these defects has been supported by anatomic investigation of the brain. When microscopically examined, the right hemisphere showed interruption of the ventral half of the visual radiation close to its origin in the lateral geniculate body. There was presumably a defect involving the upper homonymous quadrants of the left halves of the visual fields, extending probably as far as the horizontal meridians and including the macula. The functional defect to be postulated on the basis of an examination of the left hemisphere was far less extensive and was probably confined to the upper part of the temporal crescent of the right eye. Despite the defects in the upper left quadrants, the monkey would jump without hesitation from the floor to high stands or tables. Anatomic investigation of the brain in case 4 indicates that one must postulate a defect confined to the upper parts of the temporal crescents. Anatomic data on other cases are not as yet available.

In studying visually induced reactions, the question is of interest whether the sequence of reactions in multiple object tests and other test situations is determined by strong lateral tendencies. Such right or left tendencies appear in normal animals, but especially in hemianopic monkeys when series of similar objects are presented. Lateral tendencies also occur at times in cases of bilateral temporal lobectomy, but our observations in multiple object tests and other tests, in which dissimilar objects are introduced, do not support the view that strong right or left tendencies, combined with an excessively strong impulse to action, enforce on the animal a certain sequence of reactions.

The temporal lobes have been of interest chiefly because of their importance for auditory function. In studying the anatomic relationship of the medial geniculate body to the cerebral cortex, Walker [11] has found that in the rhesus monkey the medial geniculate body projects only to a small area on the superior surface of the first temporal convolution. It is of historical interest that work on the functional significance of the temporal lobes has really been concerned with this small area. In our operations no attempt was made to remove this area, since our

11. Walker, A. E.: The Primate Thalamus, Chicago, University of Chicago Press, 1938.

interest in temporal lobe functions was aroused by the discovery of one of us (Klüver) that the injection of mescaline or chemically related substances into monkeys produces peculiar chewing and licking movements as well as convulsions, in other words, symptoms resembling those found in the "uncinate group of fits" described by Hughlings Jackson and Stewart.[12] It was thought desirable, therefore, to remove the temporal lobes, including the uncus. In passing, it should be noted that the symptoms produced by mescaline are the same in the bilateral temporal monkey as in the normal monkey.

The bilateral temporal monkeys in our series did not exhibit any disturbance in auditory function if judged by the motor reactions to various sounds. Although quantitative data are lacking, it seems justifiable to assume that at least gross defects were absent. The anatomic data so far available support this view. In case 1 only the caudal tips of the medial geniculate bodies were degenerated. In case 4 the posterior one fourth or one third of the medial geniculate bodies was degenerated, the degeneration being more extensive on the right side. For several weeks, and even months, these animals do not vocalize; no sound is uttered in response to other monkeys. The monkey is likely to remain silent even if it is attacked or if the whole colony is shouting at feeding time. The vocal behavior which appears thereafter seems to differ from that of the normal monkey. The fact that the animals respond to and yet do not seem to recognize the meaning of sounds suggests the possibility of "agnosia" in the auditory field.

The possibility of a tactile agnosia must also be considered, although we failed to detect changes in cutaneous sensitivity in most cases. None of the monkeys was satisfied with touching, grasping or manipulating the objects. Seizing an object was merely preparatory to transporting it to the mouth. With the methods at our disposal, it was difficult to obtain reliable data on the gustatory and the olfactory sense, but it is noteworthy that inedible objects were never swallowed. Inedible objects were always discarded after an oral examination, although even feces was often chewed several times before being removed. Nevertheless, the type and speed of removing objects, such as feces, a piece of food soaked in quinine or a wooden or metal object, were often strikingly different. In view of the fact that the lesions involved all or the greater part of the hippocampus and uncus, it is of special interest that the "smelling" of objects and the characteristic gesture of holding an object before the nostrils represent some of the most typical reactions of the bilateral temporal monkey. It is significant that such reactions were absent in case 6, in which the olfactory tracts had been cut.

The motor reactions involved in grasping, holding, picking up and pulling in objects were essentially the same as in normal monkeys. In some cases abnormalities of gait were observed. Although the tendency to approach and contact every object seemed equally strong in all animals, there were considerable differences in the amount of spontaneous activity. All of the more active monkeys tended to perform "antics," not only when they could not get certain objects beyond reach but also when they were left to themselves in their home cages. In our previous description of case 1 it was pointed out that we frequently observed a "sequence of gesticulations, involving arms, head and most of the body."[1b] These gesticulations and similar movement patterns in other

12. Jackson, J. H., and Stewart, P.: Epileptic Attacks with a Warning of a Crude Sensation of Smell and with the Intellectual Aura (Dreamy State) in a Patient Who Had Symptoms Pointing to Gross Organic Disease of the Right Temporo-Sphenoidal Lobe, Brain **22**:534-549, 1899.

cases are difficult to describe. The many peculiar movements executed by the animal while sitting, lying, jumping or hanging from the top or sides of the cage frequently arouse the mirth of a casual observer. The monkey may repeatedly put both feet, or one foot and one hand, simultaneously behind its neck. It may jump around on the floor of the cage while holding on to one foot with one hand and then without letting the foot go may jump to the seat of the cage. In jumping from the seat to the floor, it may seize the wire mesh at the top of the cage first with its hands, then with its feet, and then may drop to the floor, landing on its hands first. It may swing and perform peculiar twists of its body while hanging with its feet from the top of the cage. It may grab one forearm with one hand and move both arms up and down. It may hang with its hands from the top of the cage and, after pulling its body through the space between its arms, may swing back and forth with its feet almost touching the floor of the cage. It may repeat such movement patterns many times and combine them in different ways. In fact, the general picture is that of a witzelsucht of the extremities.

Emotional Changes.—In the bilateral temporal monkey we find either profound changes in emotional behavior or complete absence of all emotional reactions in the sense that the motor and vocal reactions generally associated with anger and fear are not exhibited. This change in affectivity is especially remarkable in view of the fact that care has been taken to use only "wild," aggressive monkeys in this work.

The fact that the monkey approaches every object without hesitation, no matter whether it be a catcher, a large bull snake or a strange person, represents in itself a striking deviation from normal behavior. Even bodily contact with an object does not produce avoidance reactions or other forms of behavior indicative of fear. Movements, for instance, of a live animal when being examined, or other forms of sensory stimulation may, because of their suddenness, lead to retreat, but often immediately thereafter a new attempt is made to establish contact with the object.

The typical reaction of a "wild" monkey when suddenly turned loose in a room consists in getting away from the experimenter as rapidly as possible. It will try to find a secure place near the ceiling or hide in an inaccessible corner where it cannot be seen. If seen, it will either crouch and, without uttering a sound, remain in a state of almost complete immobility or suddenly dash away to an apparently safer place. This behavior is frequently accompanied by other signs of strong emotional excitement. In general, all such reactions are absent in the bilateral temporal monkey. Instead of trying to escape, it will contact and examine one object after another or parts of objects, including the experimenter, strangers or other animals. The experimenter may walk over to it, touch and stroke and even pick it up. The monkey often confines itself almost entirely to examining objects which are on or can be reached from the floor. After being attacked and bitten by another animal, it may approach this animal again and again in an attempt to examine it.

While this is the general picture of emotional behavior, individual animals present differences. Expressions of emotions, such as vocal behavior, "chattering" and different facial expressions, are generally lost for several months, but they may reappear. In some cases the loss of anger and fear reactions is complete. In case 6, for instance, the animal is restlessly active most of the time, constantly attending to and responding to numerous stimuli, never resenting any form of handling, always eager to engage in playful activities with the experimenter or to follow him around the room. In fact, it may be said that the picture of normal "wildness" has been replaced by that of "hypomania." The

bodily expressions of emotions associated with aggressive tendencies can be observed in some monkeys after a few months. Although such a monkey, with teeth bared and ears laid back, may jump toward the experimenter as if to attack him, it will merely lick or otherwise examine the fingers of the experimenter. The animal may exhibit expressions of intense emotional excitement in case the floor is swept near its cage or a wagon rolled by, but the moment the monkey is allowed to contact and to examine the broom or the wagon, the anger expressions will immediately subside. It seems that emotional behavior, when it occurs, occurs chiefly in connection with events preceding or following the oral examination of an object, especially when the attempt to contact an object is thwarted.

Changes in Sexual Behavior.—In some monkeys the increase in sexual activity is so marked and the manifestations of sexual behavior are so diverse that we are forced to include sexual changes among the symptoms produced by bilateral temporal lobectomy. Such changes are not immediately apparent. We have noticed them first three to six weeks after the operation. It should be noted that 2 of the monkeys in our series were killed before this period. Our observations are, therefore, chiefly concerned with male macaques.

The monkeys appear hypersexed, not only when with other animals but also when alone. The reactions to be recorded either are overt sexual responses or represent forms of behavior involving some sexual element. When the monkey is confined alone in a cage, the following states and activities can be observed: frequent erection of the penis, often without previous manipulation, the glans penis being clearly visible, or semierection, even while the animal is sitting quietly; long-continued licking and sucking of the penis, the animal at times apparently falling asleep with the penis in the mouth; manipulating or pulling at the penis or scrotum, even while the animal is standing; "yawning" (as seen in copulatory reactions) and, at the same time, manipulation of the genitalia while lying on the back or side; oral and manual exploration of the genitalia while the animal is in all kinds of positions, for instance, biting of the penis while swinging back and forth with the feet suspended from the top of the cage and with the hands pressed against the hindquarters; long-continued biting of the fingers, toes, feet, legs and other parts of the body; grabbing the bars of the cage and pressing the hindquarters rhythmically against them, and "presenting reactions" on approach of an observer. Grabbing the finger of the observer may be immediately followed by general bodily activity and penile erection.

Whenever other monkeys are put into the same cage, various forms of heterosexual and homosexual behavior can be observed. The monkey may, for instance, copulate almost continuously for half an hour. It may leave the female only to mount again immediately. If two bilateral temporal male monkeys are put together, sexual behavior may take forms which make it necessary to separate the animals. One of the monkeys while lying on the seat of the cage may reach with one hand toward the floor to grab the erect penis of the other monkey and practically lift the animal from the floor. The animal which is being lifted may do nothing but utter a grunt. Or one monkey may grab the tail of the other and in pulling it across the edge of the seat incidentally break the tail. While one monkey mounts the other and performs copulatory movements, the other one may be seen standing with erect penis. Or both monkeys may lie on the floor and mutually explore each other's genitalia. One monkey may ride on the back of the other and at the same time suck one of its ears. Although they frequently bite each other's legs, arms or tail, fights never develop, and injuries are merely the by-product of heightened sexual activity.

Since such striking manifestations of sexual behavior are completely absent in the normal animals of our colony and do not appear in unilateral temporal monkeys kept on the same diet and under the same conditions, or in monkeys with differently situated lesions, we feel justified in assuming that these sexual changes are dependent on removal of the second temporal lobe or simultaneous removal of both lobes.[13]

GENERAL CONSIDERATION OF BEHAVIORAL CHANGES

Munk failed to produce "psychic blindness" in rhesus monkeys, and although he thought that he had succeeded in producing it in dogs, it was subsequently shown by a number of investigators that visual disturbances and field defects could account for the behavior of the animals. We have found a picture of "psychic blindness" following bilateral temporal lobectomy in the monkey. The importance of this result lies, first of all, in the fact that such a picture can be produced by a cortical operation in animals. At the start, questions such as the duration of the symptoms or the exact nature of the lesions are of secondary importance.

In studying the various reactions and reaction tendencies, we have arrived at a group of symptoms which we may consider "typical" for the bilateral temporal monkey. We are aware that the picture may be modified by a variety of factors. The animals in the present series were studied for varying periods, ranging from three weeks to about two years from the date of the operation. They differed in age, weight, sex and other factors. Nevertheless, in all cases the typical symptoms, which we have briefly summarized under "psychic blindness," oral tendencies, "hypermetamorphosis" and emotional changes, appeared almost immediately and remained remarkably constant for the periods of observation indicated. It is true that changes occurred, but that these changes were not more marked deserves special emphasis. For instance, the experimenter could at all times touch, stroke or slap 6 of the 8 monkeys. Such treatment of the other 2 animals was not possible after several months, but their emotional behavior remained profoundly altered. Monkey 1, which was studied for about two years, tended during the last few months, in multiple object tests, to pick up food first and then to examine the remaining objects, but was inclined to pick up objects indiscriminately again when they were kept out of view until presented or when injections of mescaline were given. It

13. It is perhaps significant that in case 1 typical "presenting reactions" were frequently observed after a period of one and a half years in spite of the fact that the uterus and both ovaries had been previously removed. This animal, as well as 3 other monkeys that had had similar operations, were supplied to us by Dr. G. W. Bartelmez. Two of these animals were even "wilder" and more "vicious" than the average untamed rhesus monkey. Only 1 of these 4 animals was used in the present study (case 1).

should be remembered that many of the objects used in these tests had been presented again and again in the course of previous experiments. In brief, even the long-continued study in this case revealed little change in the general picture presented by "psychic blindness," oral tendencies, "hypermetamorphosis" and emotional changes.[13a]

In considering the polysymptomatic picture following bilateral temporal lobectomy, the question may be raised whether the various symptoms point to one basic defect or disturbance. Conceivably, any of the symptoms described may be indicative of a disturbance in some fundamental mechanism, so that all other symptoms could be understood by reference to one factor. At present, however, any attempt to reduce the variety of behavioral manifestations to one simple formula seems rather hopeless. To determine the mechanisms operative in the behavior of these monkeys further analysis is needed. Preliminary information was obtained in studying various conditioned differential reactions.

In the "form board" test, the monkey was required to react positively to a circle instead of a square. The normal monkey may learn this without even making one error if the tests are preceded by a few trials with a one hole form board. We shall briefly state the results in cases 1, 5 and 6. In case 1 training was started after removal of both temporal lobes. The animal acquired the differential response only with difficulty and after hundreds of trials. For a long time stimulus figures and food were responded to indiscriminately, but finally an errorless performance was reached. Monkeys 5 and 6, which had been trained before the operations, showed a marked disturbance of the differential response after removal of both lobes, but it was possible to reestablish the response through training. The same marked disturbance occurred in the reactions of monkey 8, which had previously been trained to respond negatively to a sound. However, when vibratory stimulation was included by use of a buzzer or a bell fastened below the floor of the cage instead of the original source of sound (a Cenco impulse counter placed at a considerable distance from the cage), the animal immediately obtained food in 100 per cent of the trials by opening the proper receptacle of the automultistimulation reaction board. Only one of the responses established preoperatively was found intact after bilateral temporal lobectomy, namely, the response in case 6 to the lighter weight in the 1,050 and 350 Gm. pair.

More important than these findings, perhaps, is the fact that we were able to demonstrate that the animals had not lost the ability to "general-

13a. In checking on possible changes in dietary habits, we recently found that the rhesus monkeys with bilateral temporal lobectomy which are still living (monkeys 6, 7 and 8) eat animal foods, such as bacon, liver sausage, boiled ham, boiled tongue, smoked whitefish, ground beef and broiled lamb chops. We have never seen normal rhesus monkeys accept such articles of diet.

ize" when responding to visual stimuli. In the "form board" tests the properties of the stimuli were changed by introducing variations in size, brightness, color and even shape (by presenting, for instance, an ellipse and a triangle instead of a circle and a square) or by substituting "figures" drawn on cardboard for the circle and the square. Despite these changes, all 3 monkeys continued to react positively to the circle or responded immediately to the curvilinear figure.

It may be said that the ability to respond to different objects in terms of such relations as "larger than," "brighter than" or "nearer than," or such properties as "angular" or "curvilinear" implies "generalizations" of a very primitive order. It can be readily understood that adaptive behavior, as long as it occurs at all, presupposes the effectiveness of such properties or the existence of such primitive forms of "generalization," and it is apparently for this reason that investigators have frequently insisted that the *Beziehungsfunktion* cannot really be destroyed by cerebral lesions.

In view of this situation, the results obtained in the Cebus monkey (case 5) are of special interest. The "form board" tests gave no evidence that the ability to "generalize" in responding to visual stimuli was impaired. At the same time, the ability to utilize objects as "tools" in obtaining food was completely lost. It is apparently one thing to recognize that a stick is "longer than" another one or "nearer than" a piece of food; it is another thing to recognize the "tool" character of a stick. As previous work indicates,[9] being "longer than" and being a "tool" are properties which become effective at different levels of adaptive behavior. At any rate, monkey 5 was unable to solve even the simplest problem in which a piece of food lying beyond reach on the floor could be obtained by using a stick lying near the food and within reach of the animal. The response consisted in repeatedly making an oral examination of the stick and again and again reaching for the food with one hand. When different objects were available at the same time, such as a stick, a sack, a wire or a leather belt, the monkey, instead of seizing one of them to obtain food in a few seconds, as it would have done in preoperative tests, repeatedly reached for the food and walked around for half an hour or longer examining one object after another. None of the objects was ever carried around. It is of great theoretic interest to learn whether these results will be confirmed by future work on suitable animals.

EFFECTS OF OTHER LESIONS

The behavioral changes following the removal of one temporal lobe were studied in 8 monkeys (cases 1 to 7 and 14) for periods ranging from about two weeks to seven months. The extirpation of one lobe

produced none of the symptoms characteristic of the bilateral temporal monkey. In some cases, however, there was a change in the direction of greater "tameness." This seems significant in view of the fact that we have failed to observe a similar change in monkeys with occipital, parietal or frontal lesions. There was no disturbance in differential responses established before the operation.

Furthermore, the forms of behavior typical of monkeys with both temporal lobes removed did not appear after (1) bilateral removal of the first temporal convolution (case 9); (2) unilateral or bilateral removal of the second and third temporal convolutions (cases 10 and 15); (3) severing the connections between the temporal and the frontal lobes (cases 11 and 12), or (4) severing the connections between the temporal and the occipital lobes (case 13). Only in case 13 was there uncertainty as to whether at least some of the symptoms existed in an attenuated form.

Of special interest are the results in case 16. The chief effect of removing the left temporal lobe subsequent to removal of both prefrontal areas was disappearance of the restlessness and the hyperactivity characteristic of the prefrontal monkey and a marked change in the direction of greater "tameness." [14]

COMMENT

In view of the fact that the anatomic study of the brains has not yet been completed, a detailed discussion of the relations between behavioral and neural mechanisms is out of the question. At this point it seems worth while, however, to relate some of the results of our behavioral analysis to data furnished by human pathology.

We may consider the outstanding characteristic of the behavioral changes following bilateral temporal lobectomy to be that they affect the relation between animal and environment so deeply. A monkey which approaches every enemy to examine it orally will conceivably not survive longer than a few hours if turned loose in a region with a plentiful supply of enemies. We doubt that a monkey would be seriously hampered under natural conditions, in the wild, by a loss of its prefrontal region, its parietal lobes or its occipital lobes, as long as small portions of the striate cortex remained intact.

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14. Spontaneous activity was registered by utilizing vacuum tube amplification. The floor of the cage was covered with pieces of galvanized iron separated by gaps of about 15 cm. A minute current passing through the body of the animal operated a relay control whenever the animal walked or ran across these gaps. In such a way the number of circling movements or other movements from one part of the cage to the other could be automatically recorded by an electric counter.

The fact that removal of both temporal lobes in the monkey may result in such profound behavior changes, particularly in the emotional sphere, becomes of special interest in view of the insistence of previous writers, such as Anglade, Takase and Marburg, that the temporal lobes in man are in some way concerned with emotions or "affective tonus." [15] The possible significance of the temporal lobes for emotional behavior has also been brought out in recent discussions of the nonolfactory functions of the "olfactory" cortex. It should be recalled that our extirpations include structures generally represented as subserving some phase of olfactory function. Herrick [16] expressed the view that the olfactory cortex may serve as a nonspecific activator for all cortical activities and that it may act on "the internal apparatus of general bodily attitude, disposition and affective tone." In studying the rhinencephalon of the dolphin, Addison [17] found that the hippocampus, fornix, mamillary bodies and habenular and amygdaloid nuclei are present, although the olfactory bulbs and tracts are lacking. Langworthy [18] made similar observations in the porpoise. It is of interest that the parolfactory cortex, which Edinger termed a center for the *Oralsinn,* was present in both forms. In the opinion of Langworthy, "the fact that the hippocampus, fornix, and mamillary bodies persist . . . suggests that they must have functions other than olfactory."

The nonolfactory functions of these structures have recently been emphasized in a different connection by Papez,[19] who attempted to find an "anatomic basis of the emotions" by correlating anatomic, clinical and experimental data of various kinds. He stated:

> It is proposed that the hypothalamus, the anterior thalamic nuclei, the gyrus cinguli, the hippocampus and their interconnections constitute a harmonious mechanism which may elaborate the functions of central emotion, as well as participate in emotional expression.

Papez suggested that "the central emotive process of cortical origin" may be built up in the hippocampus and transferred to the mamillary body and thence through the anterior nuclei of the thalamus to the cortex of the cingular gyrus, from which the process may spread to other regions in the cerebral cortex. He found "no clinical or other evidence" to support the view that these structures mediate olfactory function.

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15. von Economo, C., and Koskinas, G. N.: Die Cytoarchitektonik der Hirnrinde des erwachsenen Menschen, Berlin, Julius Springer, 1925.

16. Herrick, C. J.: The Functions of the Olfactory Parts of the Cerebral Cortex, Proc. Nat. Acad. Sc. **19**:7-14, 1933.

17. Addison, W. H. F.: On the Rhinencephalon of Delphinus Delphis, L., J. Comp. Neurol. **25**:497-522, 1915.

18. Langworthy, O. R.: A Description of the Central Nervous System of the Porpoise (Tursiops Truncatus), J. Comp. Neurol. **54**:437-499, 1932.

19. Papez, J. W.: A Proposed Mechanism of Emotion, Arch. Neurol. & Psychiat. **38**:725-743 (Oct.) 1937.

In our experiments, the cortical circuit proposed by Papez has been definitely interrupted by removal of the hippocampus. The fact that none of the typical symptoms appeared in animals in which the hippocampus was left intact may also be interpreted as lending further support to Papez' theory. As pointed out before, the behavioral reactions characteristic of the bilateral temporal monkey were absent when only the first convolution or the second and third convolutions of the temporal lobes were removed, or when the connections between the frontal and the temporal lobes or between the occipital and the temporal lobes were severed. Whether the hippocampal formation and its connections play such a decisive role in emotional behavior, as suggested by Papez, can only be determined by subsequent experimentation. To throw further light on the symptomatology of the bilateral temporal monkey, it will be necessary to study not only the effects of differently situated subtotal lesions but also the changes following a resection of the fornix or an isolated removal of the hippocampus. Herrick [16] has called attention to the fact that most ablation operations performed in connection with studies of behavior have involved only the neopallium, leaving the olfactory cortex entirely intact or but slightly injured. He pointed out the necessity for removing the various parts of the olfactory cortex in an isolated manner, although this may involve "difficult, but probably not impossible surgical operations."

Kleist [20] has advanced ideas similar to those of Papez in proposing an anatomic substratum for enteroceptive functions, i. e., drives, attitudes, personality traits, moods and emotions. Spatz [21] expressed doubt that the highly developed *Orbitalhirn* of Kleist and the primitive allocortical olfactory region are intimately related and emphasized the importance of the "basal cortex" of the temporal and the frontal lobe for personality changes. He advanced the opinion that no other disease is more important for advancing knowledge of cortical localization than Pick's disease. In this disease there are not only fundamental changes in personality and character but also such symptoms as echolalia, echopraxia and palilalia.[22] Even in the last stages of the disease the patient may still visually attend to everything that is going on and seize every object within reach to put it into his mouth.[23]

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20. Kleist, K.: Bericht über die Gehirnpathologie in ihrer Bedeutung für Neurologie und Psychiatrie, Ztschr. f. d. ges. Neurol. u. Psychiat. **158**:159-193, 1937.

21. Spatz, H.: Ueber die Bedeutung der basalen Rinde, Ztschr. f. d. ges. Neurol. u. Psychiat. **158**:208-232, 1937.

22. Benedek, L., and Lehoczky, T.: The Clinical Recognition of Pick's Disease: Report of Three Cases, Brain **62**:104-122, 1939.

23. von Braunmühl, A., and Leonhard, K.: Ueber ein Schwesternpaar mit Pickscher Krankheit, Ztschr. f. d. ges. Neurol. u. Psychiat. **150**:209-241, 1934.

In considering the "hypermetamorphosis" and "hypermetamorphic impulse to action" in the bilateral temporal monkey, we commented on the "compulsory" nature of the reactions. The question may be raised whether the lack of inhibition displayed in seizing every object and the tendency to respond to the same object again and again find their parallel in the symptomatology in cases of lesions in the human temporal lobe. It is perhaps significant that the analysis of speech disorders led Pick [24] to the view that the temporal lobes form the anatomic basis of inhibition, the absence of which leads to logorrhea, various echo symptoms (echolalia, echographia, echopraxia) and paraphasia. According to him, the speech utterances accompanying the epileptic aura or the "dreamy states" of Hughlings Jackson also involve the same mechanism of disinhibition.

In studying the similarities of catatonic and encephalitic disturbances in motility, Steiner [25] found postencephalitic children who touched and examined every object in sight by hand without uttering a word. He expressed the view that a "hypermetamorphosis" which takes the form of touching and tactually examining every object is closely related to echopraxia and echolalia. It is of interest that Leyser,[26] Lotmar [27] and others stated that "hypermetamorphosis," profound changes in affectivity and changes in sexual behavior are the outstanding symptoms in cases of epidemic encephalitis.

The fact that a picture of "psychic blindness," as described by Munk, should result from lesions of the temporal lobe is not readily explained at present. The close relation of aphasic and agnostic symptoms has been frequently emphasized. It is known from Walker's study of the thalamocortical projection of the rhesus monkey that the temporal lobe has few or no thalamic connections except from the medial geniculate body.[11] The functional significance of this observation is not clear, but it seems that the elaboration of impulses relayed from the periphery by way of the thalamus cannot be one of the chief functions of the temporal lobes. The importance of the corticifugal

24. Pick, A.: Aphasie, in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1931, vol. 15, pt. 2, pp. 1416-1524.

25. Steiner, G.: Encephalitische und katatonische Motilitätsstörungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **138**:553-561, 1922.

26. Leyser, E.: Untersuchungen über die Charakterveränderungen nach Encephalitis epidemica, Arch. f. Psychiat. **72**:552-609, 1925.

27. Lotmar, F.: Die Stammganglien und die extrapyramidal-motorischen Syndrome, in Foerster, O., and Wilmanns, K.: Monographien aus dem Gesamtgebiete der Neurologie und Psychiatrie, Berlin, Julius Springer, 1926, no. 48, pp. 1-169.

fiber connections of the temporal region, as studied by Mettler,[28] must also be considered. Niessl von Mayendorf [29] has advanced the theory that visual agnosia is due to lesions of the left macular bundle of the visual radiation or of the cortical representation of the macula in the left hemisphere. We consider it safe to assume that the picture of "psychic blindness," as found in the bilateral temporal monkey, is not due to such lesions. The anatomic investigation, for instance, of the brain of monkey 4 has clearly demonstrated that both macular bundles are intact. The behavioral tests applied to animals still living definitely suggest that visual field defects do not exist in the majority of cases.

SUMMARY

The behavioral effects of the removal of both temporal lobes, including the uncus and the greater part of the hippocampus, were studied in macaques. The monkeys exhibited the following symptoms: (1) forms of behavior which seem to be indicative of "psychic blindness"; (2) strong oral tendencies in examining available objects (licking, biting gently, chewing, touching with the lips, "smelling"); (3) a strong tendency to attend and react to every visual stimulus ("hypermetamorphosis"); (4) marked changes in emotional behavior or absence of emotional reactions in the sense that the motor and vocal reactions generally associated with anger and fear are not exhibited, and (5) an increase in sexual activity. These symptoms also appeared if the olfactory tracts were cut previous to removing both temporal lobes. Even the oral tendencies, except for the "smelling," were present.

The symptoms typical of monkeys with both temporal lobes removed did not appear after (1) bilateral removal of the first temporal convolution; (2) bilateral removal of the second and third temporal convolutions; (3) severing the connections between the temporal and the frontal lobes, i. e., duplicating the anterosuperior margin of the lesion produced by temporal lobectomy; (4) severing the connections between the temporal and the occipital lobes, i. e., duplicating the posterior margin of the lesion produced by temporal lobectomy. The symptoms also did not appear after unilateral temporal lobectomy, except that there was in some cases a change in the direction of greater "tameness." This "tameness" was also observed when after previous extirpation of both prefrontal areas one temporal lobe was removed.

Differential reactions to visual stimuli established preoperatively were seriously disturbed after bilateral temporal lobectomy, but it was possible to reestablish the response through training. The ability to "generalize" in responding to visual stimuli did not seem to be impaired.

28. Mettler, F. A.: Corticifugal Fiber Connections of the Cortex of Macaca Mulatta: The Temporal Region, J. Comp. Neurol. **63**:25-47, 1935.

29. Niessl von Mayendorf, E.: Beiträge zur Lehre von der Seelenblindheit: VIII, Ztschr. f. d. ges. Neurol. u. Psychiat. **159**:326-344, 1937.

HISTOPATHOGENESIS OF CEREBRAL ABSCESS

FRANCIS A. CARMICHAEL JR., M.D.*
KANSAS CITY, MO.
AND
JAMES W. KERNOHAN, M.D.
AND
ALFRED W. ADSON, M.D.
ROCHESTER, MINN.

Among the earliest reports dealing with cerebral abscesses is that of Morand,[1] who in 1751 described a successfully treated "putrid ulcer in the brain." Toynbee [2] as early as 1850 and in the following years, reported the observations at necropsy in several cases of abscess of the brain apparently of otitic origin and remarked on their association with a molluscous tumor in the external meatus of the ear, although it is not clear that he understood the relation between the two. However, it was not until the advent of Macewen's classic work [3] in 1893 that abscess of the brain was considered as anything but a pathologic curiosity.

INCIDENCE

Pitt,[4] in 1890, collected 57 cases of pyogenic intracranial disease in a series of 9,000 necropsies. Schorstein,[5] in 1909, encountered 21 cases of abscess of the brain in 3,700 necropsies, in 19 of which the abscess was secondary to pulmonary disease alone. In 1931 Evans [6] collected 194

* Fellow in Neurosurgery, the Mayo Foundation.

From the Sections on Pathologic Anatomy and Surgical Pathology (Dr. Kernohan) and the Section on Neurologic Surgery, the Mayo Clinic (Dr. Adson).

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1. Morand, cited by Ballance.[36]

2. Toynbee, J.: Examination of the Petrous Portion of the Temporal Bone in a Case of Disease of the External Auditory Passage, with Suppuration of the Brain, Tr. Path. Soc. London **2**:272-273 (May 6) 1850.

3. Macewen, W.: Pyogenic Infective Diseases of the Brain and Spinal Cord, Meningitis, Abscess of Brain, Infective Sinus Thrombosis, New York, Macmillan & Co., 1893.

4. Pitt, G. N.: The Goulstonian Lectures on Some Cerebral Lesions, Brit. M. J. **1**:643-647 (March 22) 1890.

5. Schorstein, G. I.: The Schorstein Lecture on Abscess of the Brain in Association with Pulmonary Disease, Lancet **2**:843-852 (Sept. 18) 1909.

6. Evans, W.: The Pathology and Aetiology of Brain Abscess, Lancet **1**: 1231-1235 (June 6); 1289-1292 (June 13) 1931.

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cases of cerebral abscess in a consecutive series of 14,534 necropsies. That the incidence of this condition, as expressed in the preceding figures, is of direct clinical and surgical importance may be appreciated from the statement by Swift [7] that in 1 of 6 cases in which mastoidectomy was performed there is a complicating intracranial lesion. In support of this statement, Dickie [8] found that of 3,918 cases of suppuration of the middle ear intracranial complications occurred in 85, in 15 of which there were abscesses of the brain. In a study of 534 cases of intracranial complications secondary to disease of the air sinuses, Burger [9] found abscesses of the brain in 176. Engelmann [10] noted the occurrence of abscess of the brain in 5 of a series of 120 cases of suppurative frontal sinusitis.

ETIOLOGIC CONSIDERATIONS

From the earliest studies concerning abscess of the brain it became apparent that this condition was associated frequently with other definite pathologic states. First and foremost among those was otitis media. Weil [11] estimated that 40 per cent of abscesses of the brain are so derived. It is generally agreed that the chronic type of suppuration of the middle ear is the more important factor, accounting for about 80 per cent of such abscesses, whereas the acute type is responsible for the remaining 20 per cent.

Next in order of importance come pathologic states of the lungs, of which bronchiectasis is the principal contributor, followed by pulmonary empyema, abscess and gangrene.

In analyzing the cause of death in 63 cases of bronchiectasis, Schorstein [5] found that 17 patients died of bronchopneumonia whereas 13 died of abscess of the brain, cerebral abscess thus being second in the list of causes of death from this relatively common condition. This peculiar relationship between cerebral and pulmonary disease is not confined to the consideration of abscess alone but is also witnessed in the frequency and facility with which metastasis to the cerebrum occurs from carcinoma

7. Swift, G. W.: The Differential Diagnosis Between Septic Meningitis, Brain Abscess and Lateral Sinus Thrombosis Complicating Mastoiditis, Ann. Otol., Rhin. & Laryng. **36**:669-674 (Sept.) 1927.

8. Dickie, J. K. M.: A contribution to the Study of Brain Abscess, Ann. Otol., Rhin. & Laryng. **31**:683-713 (Sept.) 1922.

9. Burger, H.: Die endokraniellen Komplikationen der Nasennebenhöhlenentzündungen, in Denker, A., and Kahler, O.: Handbuch der Hals-Nasen-Ohrenheilkunde, Berlin, Julius Springer, 1926, vol. 2, pp. 898-949.

10. Engelmann, cited by Warrington, W. B.: Critical Review: Abscess of the Brain, Quart. J. Med. **11**:141-164 (Jan.) 1918.

11. Weil, A.: A Text-Book of Neuropathology, Philadelphia, Lea & Febiger, 1933.

of the lung. Schorstein expressed the opinion that this relationship is intimately concerned with the immunity of the organism and that for some unaccountable reason the brain, unlike the other bodily tissues, fails to build up an adequate immunologic defense to infections of the lung. Adam [12] drew attention to the fact that both bronchiectasis and abscess of the brain are associated frequently, if not usually, with sinusitis, and he concluded that they are derived from a common origin. Gardner [13] and Groth [14] postulated that the mechanics of coughing, which act is so often a feature of bronchiectasis, is important in causing engorgement and venous congestion of the cerebral vessels and thereby contributes to the inception of cerebral abscess. Eagleton [15] expressed himself in favor of the hypothesis that such abscesses are of thrombotic or venous rather than of embolic origin.

Next in frequence of association with abscess of the brain come other chronic focal infections, such as osteomyelitis and sinusitis, which frequently produce cerebral abscess. Closely allied to this group are acute and chronic systemic infections, such as septicemia and endocarditis, all of which conditions seemingly accomplish their effects by transportation of bacteria or septic emboli via the blood stream. Of the septicemic states resulting in cerebral abscess, those derived from furunculosis, carbunculosis and pyoderma are comparatively prominent. Endocarditis is singular in that it results in abscess of the brain much less frequently than would be expected from the early literature. This inconsistency has been remarked on by Parker,[16] Schorstein [5] and others. More recent studies have shown a higher incidence of involvement of the brain in septic endocarditis.

Added to the foregoing list of conditions particularly predisposing to cerebral abscess is another group concerning which reliable statistics are wanting but which seems from the present study and from isolated reports of cases in the literature to be of considerable importance. This group includes both acute and chronic infections of the head and face other than those which have been previously mentioned. Of these, infections in and about the orbit most consistently produce cerebral abscess. In the series studied there were 3 such cases, and similar cases

12. Adam, J.: Is Chronic Maxillary Sinusitis a Cause of Bronchiectasis? J. Laryng. & Otol. **40**:172-173 (March) 1925; Note on the Connection of Brain Abscess with Bronchiectasis, ibid. **41**:93 (Feb.) 1926.

13. Gardner, W. J.: Metastatic Abscesses of the Brain of Pulmonary Origin: A Report of Two Cases, Arch. Neurol. & Psychiat. **19**:904-908 (May) 1928.

14. Groth, W., cited by Parker.[16]

15. Eagleton, W. P.: Brain Abscess from the Standpoint of the Otolaryngologist, Laryngoscope **40**:336-356 (May) 1930.

16. Parker, H. L.: Metastatic Abscess of the Brain: A Clinical Study, Am. J. M. Sc. **180**:699-711 (Nov.) 1930.

have been reported by Miller [17] and by Mathieu and Péron.[18] Of Turner and Reynolds' series [19] of 55 cases, infections of the face accounted for the condition in 4.

Housden [20] and others reported cases of abscess following acute tonsillitis. Thompson,[21] who reported a case of abscess of the brain following extraction of a tooth, stated that 2 other such cases have been reported in the literature. Ersner and Pressman [22] described a case of abscess of the brain following primary Vincent's infection of the nose.

The exact mode by which any one of the aforementioned conditions gives rise to cerebral abscess has been the subject of long and continual controversy and has led to needlessly complex classifications of abscess of the brain on an etiologic basis. Therefore, there is offered here a modified classification which, although not original, appears to embrace all the possible etiologic factors in a simple and logical sequence.

1. Direct implantation
   - (*a*) Trauma
     - (1) Penetrating wounds
     - (2) Fracture of the skull
   - (*b*) Surgical means
2. Contiguous extension
   - (*a*) Direct suppurative extension
   - (*b*) Extension via blood vessels
     - (1) Phlebitis
     - (2) Thrombosis
     - (3) Embolism

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17. Miller, G. V.: Injury to the Eye, Complicated with Abscess of the Brain and Terminating Fatally: Autopsy; Two Cases, Brit. J. Ophth. **1**:751-754 (Dec.) 1917.

18. Mathieu, P., and Péron, N.: Les abcès du lobe frontal à porte d'entrée faciale, Paris méd. **61**:269-272 (Oct. 2) 1926.

19. Turner, A. L., and Reynolds, F. E.: Intracranial Pyogenic Diseases: A Pathologic and Clinical Study of the Pathways of Infection from the Face, the Nasal and Paranasal Air-Cavities, Edinburgh, Oliver & Boyd, 1931.

20. Housden, E. G.: Cerebral Abscess Following Acute Tonsillitis, Brit. M. J. **1**:1158 (June 29) 1929.

21. Thompson, L. E.: A Fatal Case of Brain Abscess from Vincent's Angina Following Extraction of a Tooth Under Procaine Hydrochloride, J. A. M. A. **93**: 1063-1065 (Oct. 5) 1929.

22. Ersner, M. S., and Pressman, J. J.: Primary Vincent's Infection of the Nose with Secondary Abscess of the Frontal Lobe: Report of a Case, Arch. Otolaryng. **14**:818-822 (Dec.) 1931.

(*c*) Extension via Virchow-Robin spaces
  (1) Perivasculitis
  (2) Perivascular stasis
  (3) Alterations in pressure of cerebrospinal fluid

(*d*) Extension by preformed paths
  (1) Nerve sheaths
  (2) Foramens

3. Metastatic extension
  (*a*) Without antecedent trauma
  (*b*) With antecedent trauma

4. Origin and mode of extension undetermined

In this classification the contributing factors listed in group 1 require little explanation. It is evident that the introduction of foreign and infective material directly into the cerebral parenchyma by projectile or other wounds may contribute directly to the formation of abscess. Likewise, simple fracture is contributory by opening up potentially and actually infected air sinuses, thereby exposing the brain by consequent laceration of the dura and arachnoid. Of course, surgical implantation of the infected material within the brain should be a preventable factor. That this mode results from ill advised and promiscuous probing of the brain through septic approaches with much greater frequency than is generally suspected can scarcely be doubted after careful study of many of the operative reports in the literature.

It is in the consideration of the second group of etiologic modes that one is confronted with a controversy which has occupied a large field of research on abscess of the brain. When abscess arises from direct extension of the suppurative process from an adjacent site, so that bone, dura, arachnoid and pia are traversed by the process and the cerebral parenchyma is entered, one is faced with realism which does not demand speculation. On the other hand, when cerebral abscess is derived from an adjacent focus without the invasion or destruction of intervening tissues or any apparent pathologic connection between the primary and the secondary focus, speculation must be permitted to explain the phenomenon. Macewen [8] led the field by postulating that infective material might be conveyed "by a thrombus extending through the veins into the pia or the brain." This he thought might occur in two major ways, either by a process of extension along the vessel in which the flow was not disturbed, or by a reversal of the flow of blood in a venous channel, due to stoppage of the current at some distal point. He also mentioned that infective matter might also be conveyed by the perivascular spaces.

Eagleton [23] stressed retrograde thrombophlebitis as the causative factor in the majority of abscesses which he termed "adjacent." He also admitted that in a certain number of cases the infection is transported by the perivascular spaces, but he expressed the opinion that in such instances the perivascular space is passively infiltrated and takes no active part in the transportation by reason of its circulation of cerebrospinal fluid.

Atkinson,[24] as opposed to Eagleton,[23] stressed the perivascular route as most common and relegated the mechanism of retrograde thrombophlebitis to a place of secondary importance. In 13 of 16 patients he attributed the lesions to the perivascular mode of spread. He explained this spread, which must be against the direction of the current of cerebrospinal fluid in the perivascular spaces, by a reversal of flow due to the increased intracranial tension resulting from leptomeningitis. He stated that "perivasculitis on the surface and extending down into the fissures is seen in all specimens of this type, whether the case be one of cerebral or cerebellar abscess." This statement is, of course, true if one examines a related portion of the cortex. In this instance it is extremely difficult to distinguish cause and effect, and it might be well to mention that the same type of perivasculitis has been encountered repeatedly in this study in conjunction with abscesses of known metastatic origin, in which the question of contiguous extension did not arise or could not be considered as playing any part in the process. However, it is not doubted that this mode of transmission does exist in a certain number of cases. Atkinson, again, in speaking of the contiguous "stalk," said that his studies suggested that "in all cases of adjacent brain abscess there is a point of entry of infection to be found in the dura." He observed such a portal of entry in half of the cases which he reported. He cited Körner as having found such a portal in 38 of 40 cases studied. Eagleton estimated that this pathologic condition occurred in only 4 per cent of the cases. In the present series of 75 brains containing cerebral abscesses such a "stalk" was not encountered either macroscopically or microscopically in any instance. However, in many instances the dura was not available for study, and in others the "stalk" may have been obliterated by the process itself or by the subsequent operative procedure.

Disregarding, for the moment, the exact nature of transmission and implantation of infected material, there arises the question concerning which portion of the cerebral parenchyma is most vulnerable to the development of abscess. Atkinson [24] asserted that the focus begins in a

23. Eagleton, W. P.: Brain Abscess: Its Surgical Pathology and Operative Technic, New York, The Macmillan Company, 1922.

24. Atkinson, E. M.: Abscess of the Brain: Its Pathology, Diagnosis and Treatment, London, Medical Publications, Ltd., 1934.

stratum immediately below the cortex, which he termed the "avascular zone." He expressed the opinion that the terminal branches of both the central and the cortical arteries were end arteries. This view was upheld by Orr [25] and by Duret.[26] However, the concept was dealt a severe blow by the studies of Pfeifer,[27] Cobb [28] and his pupils and Lorente de Nó.[29] Pfeifer demonstrated conclusively the presence of rich anastomoses between the cortical and the central vascular system of the brain. Cobb repeatedly emphasized the absence of such end arteries in the rabbit's brain. Lorente de Nó, a pupil of the Vogts asserted that the capillary network could be traced continuously from the olfactory bulb to the occipital cortex. However, it is obvious from these studies that some portions of the brain have relatively less vascular supply than others and that the region beneath the cortex referred to by Atkinson as the "avascular zone" is in reality less well supplied than the cortex. Just what relation this fact has to the site of predilection is difficult to estimate.

Many authors have mentioned the possibility of the transference of infected material by way of the lymphatic system. It is sometimes difficult to ascertain whether they referred to the perivascular circulation of Virchow and Robin as the lymphatic system of the brain or to the general systemic lymphatic system. In this regard, it is probable that Turner and Reynolds [19] were correct in saying that it seems anatomically impossible for infection to reach the brain by way of the actual lymphatic system.

Extension along preformed paths seems to require less explanation than spread along the pathways already considered. The possibility of extension along nerve sheaths seems logical, but it is difficult of either proof or refutation. This extension might occur in two ways: by involvement of the accompanying vessels or by extension in one manner or another by way of the subarachnoid space in the case of such nerves, notably the optic, olfactory and trifacial, as are invested for a certain portion of their course by a continuation of the subarachnoid space. The studies of Cushing [30] and his pupils, particularly Weed,[31]

25. Orr, D.: Further Experimental Work on Bacterially-Produced Nervous Tissue Lesions, J. Neurol. & Psychopath. **11**:97-110 (Oct.) 1930.

26. Duret, C., cited by Orr.[25]

27. Pfeifer, R. A.: Die Angioarchitektonik der Grosshirnrinde, Berlin, Julius Springer, 1928.

28. Cobb, S.: The Cerebrospinal Blood Vessels, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 2, pp. 575-610.

29. Lorente de Nó, R.: Ein Beitrag zur Kenntnis der Gefässverteilung in der Hirnrinde, J. f. Psychol. u. Neurol. **35**:19-27 (Oct.) 1927.

30. Cushing, H.: Studies in Intracranial Physiology and Surgery: The Third Circulation; the Hypophysis; the Gliomas, London, Oxford University Press, 1926.

31. Weed, L. H.: Experimental Studies of Intracranial Pressure, A. Research Nerv. & Ment. Dis., Proc. **8**:25, 1929.

and those of Schaltenbrand and Bailey [32] are compatible with this hypothesis.

Foramens, on the other hand, figure chiefly from the standpoint of the structures which they transmit; otherwise they act chiefly as points of least resistance for the direct extension of a contiguous suppurative process. Mixter [33] recently reported a case of actinomycotic abscess in which, in his opinion, the cerebral focus was reached by way of nerve sheaths and foramens.

Metastatic transmission of infection in cases in which the brain is concerned seems to differ little from the process which occurs in other organs. Infarction with consequent softening probably provides a suitable foothold for the organisms transmitted. Essick [34] pointed out that the stages of white, red and yellow softening so often mentioned by older authors are perhaps due only to various stages in the extravasation and decomposition of erythrocytes. Just what part trauma may play in metastatic implantation of infected material is an interesting speculation, in view of the work of Malinowski, who, according to Southard,[35] showed in 1891 that abscess of the brain invariably occurred in dogs the brains of which had been deliberately traumatized ten days prior to an intravenous injection of pyogenic bacteria. However, such abscesses occasionally could be produced by the intravenous injection of pyogenic bacteria into dogs the brains of which had not been subjected previously to traumatism.

Lastly, we approach a somewhat too large group of abscesses of the brain in which an antecedent history of infection cannot be detected and in which, consequently, a hypothesis of the mode of transmission cannot logically be postulated. Ballance [36] asserted that "brain abscess is never a primary disease." From the concepts which we have just reviewed this seems correct. However, one must admit that, try as one may, there will be, for the time being at least, cases in which the most minute examination will fail to disclose a source of the abscess. In these instances the only presumption is that the mode of transmission was metastatic and that one has failed to ascertain the source.

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32. Schaltenbrand, G., and Bailey, P.: Die perivaskuläre Piagliamembran des Gehirns, J. f. Psychol. u. Neurol. **35**:199-278 (March) 1928.

33. Mixter, W. J.: Brain Abscess from the Standpoint of the Brain Surgeon, Laryngoscope **40**:357-364 (May) 1930.

34. Essick, C. R.: Pathology of Experimental Traumatic Abscess of the Brain, Arch. Neurol. & Psychiat. **1**:673-704 (June) 1919.

35. Southard, E. E.: Brain Abscess, in Osler, W., and McCrae, T.: Modern Medicine: Its Theory and Practice, Philadelphia, Lea & Febiger, 1915, vol. 5, pp. 378-386.

36. Ballance, C. A.: A Lecture on Abscess of the Brain, Clin. J. **40**:273-285 (Aug. 7) 1912.

BACTERIOLOGIC CONSIDERATIONS

As in the case of abscess elsewhere in the body, it is generally considered that any one of the pyogenic group of bacteria is capable of producing cerebral abscess. Most of the discussions of the bacteriologic factors related to this condition are centered around the assertion by Neumann [37] and Ghon [38] that the formation of the "capsule" is due to the activity of a gram-positive diplococcus, whereas anaerobic organisms give rise to ill defined abscesses. Definite studies concerning this question were not made in the present investigation since only the histologic processes involved in the formation of the limiting membrane were considered. On the other hand, Pilot [39] asserted that "putrid abscesses are always due to mixed bacteria." We can recall at least 2 instances in which an abscess yielded Escherichia coli in pure culture and the abscesses were fairly well delimited. Staphylococcus aureus often has been held solely responsible for the production of abscesses of the brain.

EVOLUTION OF THE LESION

In the course of this study, 60 brains that contained cerebral abscesses were intensively studied, both grossly and microscopically. Of this group, many contained multiple abscesses, in which cases several abscesses were studied independently, so that the total number of abscesses studied greatly exceeded the number of brains.

Cases of purulent meningitis were not considered, and when this condition existed concomitantly with abscess only the status of the intracerebral lesion was carefully studied. The precise technic employed for these methods was that outlined by Kernohan.[40]

Heretofore it has been the custom of many observers to describe an abscess of the brain pathologically as a static and unvarying entity. Often such accounts have been confined to descriptions of a singular, comparatively well advanced abscess, or an "encapsulated" abscess, which is the term generally used. Often the impression may be gained that such a description is applicable to any or all abscesses, no account being taken of the developmental cycle of the lesion in question.

It is apparent from the outset that an abscess does not have its origin *de novo* in the tissues of the brain, but rather arises slowly from a microscopic focus and progresses usually regularly, although occasionally irregularly, to a stage of development in which, owing to a certain degree

37. Neumann, H., cited by Atkinson.[24]

38. Ghon, A.: Zur Aetiologie der otogenen Hirnabszesse, Beitr. z. path. Anat. u. z. allg. Path. **87**:222-228 (June 27) 1931.

39. Pilot, I.: Putrid Abscess of the Brain, Arch. Neurol. & Psychiat. **28**:733-734 (Sept.) 1932.

40. Kernohan, J. W.: Preparation of Neurologic Material for Histologic Study, Am. J. Clin. Path. **4**:410-425 (Sept.) 1934.

of delimitation, it deserves the distinction of the term "abscess" in its common sense.

In the description in the pages to follow, it will be attempted to take cognizance of this process and, in so far as possible, to relate the chain of associated events in cinematographic fashion. Such a description, of course, would be impossible unless it were burdened with an unwarranted number of photomicrographs; thus, of necessity, in parts it may seem presumptive. To facilitate clearness of description, the process will be divided into arbitrary stages, with the understanding that each stage is to be considered as almost imperceptibly merging with the preceding and succeeding stages. In this instance these stages are delineated without regard to the chronologic or symptomatic progress of the lesion, but are so chosen because each one represents the advent of a new element or system of elements which plays a dominant role in modifying the existing picture.

The following stages are chosen for purposes of description: Phase I: Focal necrosis; microgliosis. Phase II: Primary delimitation; fibrosis. Phase III: Secondary delimitation; astrogliosis. Phase IV: Repair; vascularization.

Phase I: Focal Necrosis; Microgliosis.—Globus and Horn [41] stated: "The earliest appearance of an abscess of the brain is that of a small circumscribed area crowded with bacteria, numerous polymorphonuclear leukocytes, leukocytes, lymphocytes, red blood cells and disintegrating nerve elements." Such a lesion is shown in figure 1 *a* and *b*. Figure 1 *a* represents a section of an abscess occurring two years after a severe basofrontal fracture which was complicated by persistent draining sinuses. Figure 1 *b* shows a section of an abscess which developed six weeks after lobar pneumonia and hydrothorax, which required rib resection. Both patients were men aged 28, and both died soon after admission and before exploration was accomplished. The exact manner of inauguration of the abscesses does not concern us now, but from their situation and contour we can intimate that each focus occurred along the course of a blood vessel and may have arisen by any one of the methods previously discussed.

Hematogenous Elements: The outstanding feature of these lesions was the central necrotic core, composed of myriads of polymorphonuclear leukocytes, lymphocytes, monocytes and gitter cells. These cells may have gained their position by escaping from the lumens of blood vessels in the region of the vessel involved, or they may have escaped from the perivascular space of that vessel before some catastrophe interfered with its functional and morphologic integrity. They appeared to have migrated toward the central lesion.

In figure 1 *b* the central lesion is surrounded by a rosette of similar areas infiltrated with hematogenous elements. That a greater or lesser number of these surrounding areas may coalesce with the central one is logical and depends probably on the relative balance between the virulence of the organism and the resistance of the tissue.

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41. Globus, J. H., and Horn, W. L.: Inherent Healing Properties of Abscess of the Brain: Clinico-Anatomic Survey of Fifteen Verified Cases, Arch. Otolaryng. **16**:603-660 (Nov.) 1932.

Blood Vessels: In both *a* and *b* of figure 1 four simultaneously existing reactions of the vessels are observed: namely, hyperemia; perivascular infiltration; occlusive endarteritis and endophlebitis, and hemorrhage.

Infiltration of the perivascular spaces of Virchow and Robin by all sorts of hematogenous elements was a predominating feature in this phase of abscess formation, just as it is in many other types of cerebral inflammation. Apparently, hyperemia in some instances had reached the degree at which the volume of blood and other cellular elements no longer could be contained within the vessel and rupture had occurred, with consequent extravasation of cellular elements throughout the cerebral parenchyma. No doubt some such cells escaped by diapedesis before rupture occurred. Toxic influences may have contributed by acting on the endothelium. Figure 2 affords a particularly good view of a vessel cut

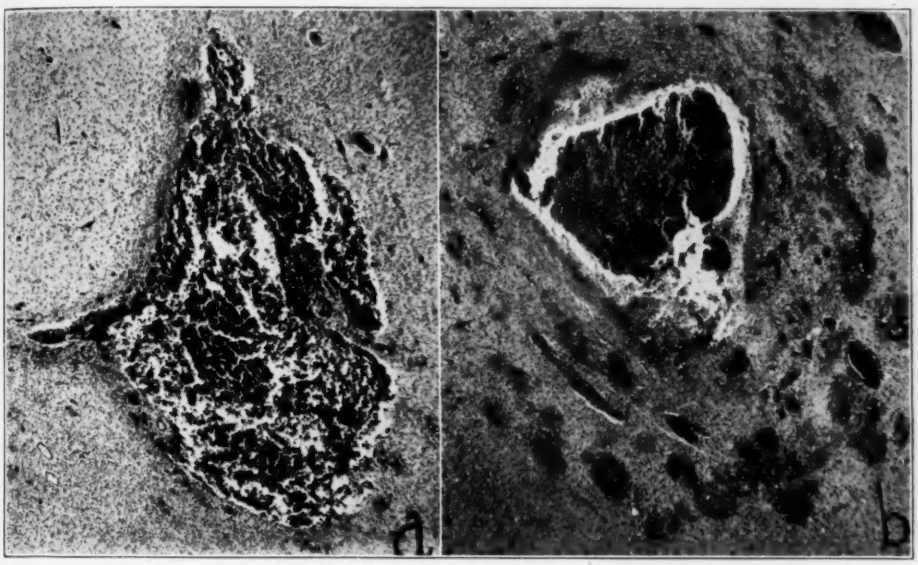

Fig. 1.—In *a* is the necrotic center of an early abscess, showing a collection of polymorphonuclear leukocytes, lymphocytes, erythrocytes and bacteria; in *b*, a lesion of same age as that in *a*, showing a surrounding rosette of hemorrhagic areas, hyperemia and vascular proliferation.

longitudinally, showing a mild form of cellular congestion in a moderately remote vessel. Endothelial cells can be seen wandering out into the tissue. These endothelial nuclei in many instances were morphologically indistinguishable from nuclei appearing in cells which otherwise had the appearance of gitter cells. The striking proliferation of the endothelium that lines the lumen of vessels and the membrane lining the Virchow-Robin spaces is also shown. In some instances this process had progressed to absolute occlusion of the vessel. This phenomenon undoubtedly facilitates expansion of the lesion by contributing adjacent areas of infarction and devitalization to the central lesion.

Microglia: It is generally admitted that the earliest participants in the activity of inflammation derived from the cerebral elements themselves are the microglia cells. In figure 3 they are seen in great profusion wandering from the adjacent

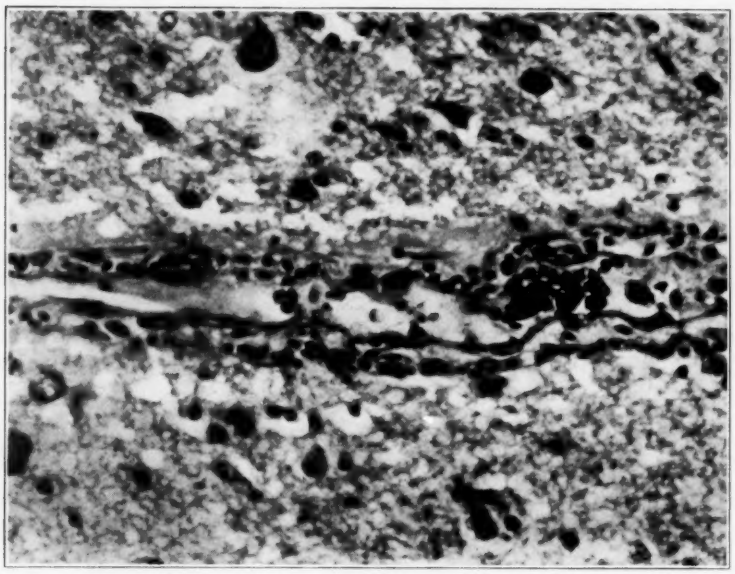

Fig. 2.—Longitudinal section of a vessel showing extreme congestion of the perivascular space, proliferation of the lining endothelial cells and their migration. The small nuclei are lymphocytes. The large vacuolated cells are gitter cells. Hematoxylin and eosin; × 290.

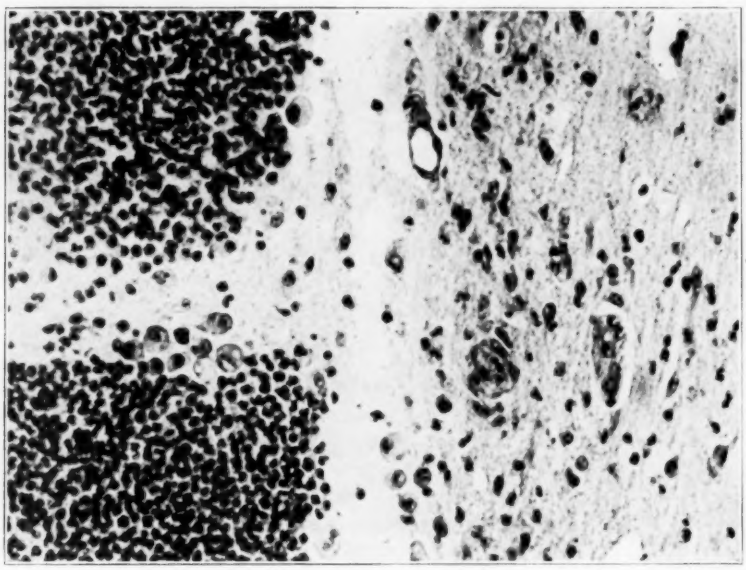

Fig. 3.—Invasion of the necrotic core of an abscess by a stream of actively phagocytosing gitter cells. Within these cells are erythrocytes, debris and fat vacuoles. The marginal vessels show a high degree of endothelial proliferation. One vessel seems occluded. The smaller nuclei are lymphocytes and rod forms of microglia. Hematoxylin and eosin; × 250.

tissue toward and into the necrotic center of the lesion. It can be observed that they have engulfed all manner of tissue debris and erythrocytes. These microglia cells are round or oval and are usually larger than any other cells that participate in the process, and they are recognized easily by the granular or apparently vacuolated appearance of their cytoplasm and by their vesicular nuclei, which usually contain a prominent nucleolus. These cells when stained with sudan III show that the vacuoles are composed of droplets of fat. The concentration of nuclei adjacent to the necrotic region, largely due to multiplication of these cells, is easily appreciated by glancing at figure 1.

For elucidation of this group of cells (microglia) one is chiefly indebted to del Rio-Hortega [42] and his pupils. Del Rio-Hortega, in a study of the cells of Cajal's so-called third element, described two independent types, the oligodendrocytes, which he showed to be of ependymal (ectodermal) origin, and the microglia cells, which are of mesodermal origin. He further related the microglia cells to the gitter cells first described by Gluge [43] in 1841, by showing that the former were the precursors of the latter. He then elucidated the intermediate, irregular, globular, rod and tuberous forms of these cells. Subsequent experiments by Russell,[44] Carmichael,[45] Wilson,[46] Macklin and Macklin,[47] Hortega and Penfield [48] and a host of others have contributed to the establishment of these views by emphasizing the early participation of microglia cells in inflammatory reactions of the brain.

Lesions of the early type, such as have just been described, have been described by other authors, notably Diamond [49] and Kimmelstiel.[50] To estimate the age of such a lesion there are no definite criteria other than those of Carmichael, who noted the appearance of microglia cells a few hours after sterile puncture wounds had been made in rabbit brains. Macklin and Macklin, making studies on rats with intravital dyes, estimated that the height of the reaction occurred at about the sixth day. Del Rio-Hortega and Penfield,[48] in similar experiments on monkeys, estimated the cells to be most abundant at about the twelfth day. Del Rio-Hortega has shown that the presence of fat in the gitter cells can be confirmed within forty-eight hours. Therefore, as we noted an abundance of phagocytic microglia cells

42. del Rio-Hortega, P.: Microglia, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 2, pp. 481-534.

43. Gluge, G.: Abhandlungen zur Physiologie und Pathologie, Jena, F. Mauke, 1841, pp. 30 and 35.

44. Russell, D. S.: Intravital Staining of Microglia with Trypan Blue, Am. J. Path. **5**:451-458 (Sept.) 1929.

45. Carmichael, E. A.: Microglia: An Experimental Study in Rabbits After Intracerebral Injection of Blood, J. Neurol. & Psychopath. **9**:209-216 (Jan.) 1929.

46. Wilson, R. B.: Brain Repair, Arch. Neurol. & Psychiat. **15**:75-84 (Jan.) 1926.

47. Macklin, C. C., and Macklin, M. T.: A Study of Brain Repair in the Rat by the Use of Trypan Blue, with Special Reference to the Vital Staining of the Macrophages, Arch. Neurol. & Psychiat. **3**:353-393 (April) 1920.

48. del Rio-Hortega, P., and Penfield, W.: Cerebral Cicatrix: The Reaction of Neuroglia and Microglia to Brain Wounds, Bull. Johns Hopkins Hosp. **41**:278-303 (Nov.) 1927.

49. Diamond, I. B.: Changes in the Brain in Pyemia and Septicemia, Arch. Neurol. & Psychiat. **20**:524-536 (Sept.) 1928.

50. Kimmelstiel, P.: Ueber Viridans-Encephalitis bei Endocarditis lenta, Beitr. z. path. Anat. u. z. allg. Path. **79**:39-68, 1927.

in the lesions just described, in which some showed inclusions of fat and others did not, it seems that these lesions must have been about two to four days old.

Oligodendroglia: In this, as in other phases of abscess formation, it was noted that oligodendroglia cells played an inconspicuous role. In some remote regions there was a slight increase in their concentration, where they had taken up their position as satellites surrounding nerve cells which apparently had already undergone pathologic change.

Astroglia: Like the oligodendrocytes, the astrocytes had not yet assumed an important role. Those in relation to vessels which had suffered severe alteration seemed to have disappeared, whereas others showed neither reaction nor degeneration.

Nerve Cells: Nerve cells were not seen in the vicinity of the lesions which we have used for illustrative purposes. However, nerve cells at a distance of

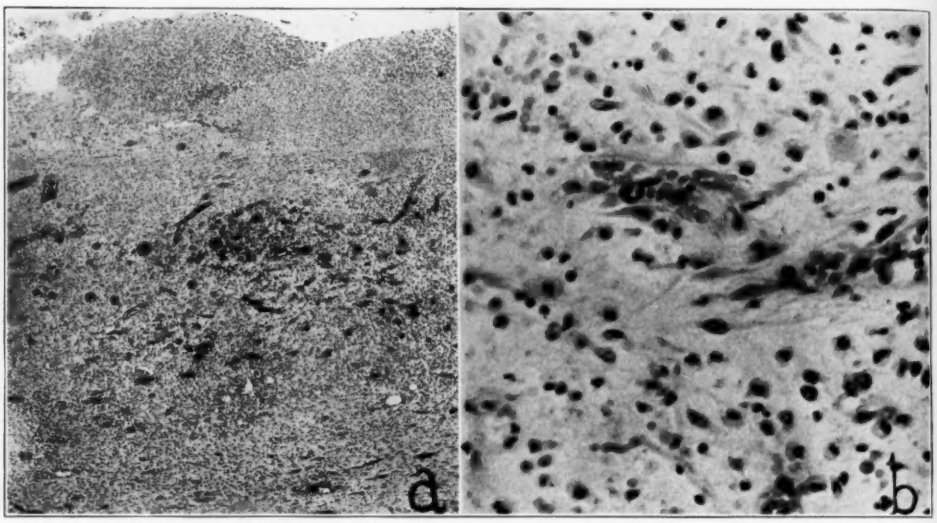

Fig. 4.—In *a* is an abscess in phase II, showing the three principal layers, which from top to bottom are: (1) central zone of necrosis; (2) layer of hyperemia and fibroblastic proliferation, and (3) broad, ill defined layer of early astrocytic proliferation. × 20. In *b* is a higher magnification (× 250) of the section in *a*, showing proliferation of fibroblasts in the hyperemic zone. Gitter, rod and irregular forms of microglia are numerous, as well as many cells of the lymphocytic series and extravasated erythrocytes. Hematoxylin and eosin.

one or more field diameters from the lesion did not show their processes well; the cytoplasm was more granular than normal, and they were surrounded by more than the usual number of satellitic oligodendrocytes. This is generally regarded as indicative of nonspecific degenerative change.

An abscess, in the phase just described, is composed of only two recognizable layers: (1) the central necrotic core and (2) the vague, ill defined region of hyperemia and microgliosis.

Phase II: Primary Delimitation; Fibrosis.—In considering a more advanced stage of abscess, one notes, as in figure 4 *a*, that although the reaction is greatly

extended in scope it is altered only in detail. Sections shown in figure 4 *a* and *b* were obtained from a patient who had suffered progressive paraparesis for thirteen years. Signs of increased intracranial pressure had been evident for only two weeks after a recent head cold. The patient died before operation was accomplished. It is doubtful whether the abscess itself was responsible for the long neurologic history.

Hematogenous Elements: The central necrotic zone was composed of numerous polymorphonuclear cells, of which many were recognizable as such and many more were disintegrated and represented by nuclear fragments or were totally unstained. The background of the necrotic center was amorphous. Here and there disintegrating erythrocytes and microglia cells could be seen.

Blood Vessels: In figure 4 *a* hyperemia is also an outstanding feature. Perivascular cuffing in the most adjacent vessels is not as outstanding in figure 5 as in the sections previously described, but it was noted in like degree in the vessels more distant from the necrotic zone. Endarteritis and endophlebitis were not as pronounced as in the initial stage, the reason being that the vessels which had been most severely involved had been included in the process and had contributed to its enlargement. However, perivasculitis, that is, proliferation of the tissue lining of the space of Virchow and Robin, was even more prominent at this stage of development of the abscess than in the initial stage. This will be considered more in detail later.

Microglia: The participation of mesodermal elements in this phase is illustrated fairly well in figure 4 *b*. They could be seen throughout the tissue adjacent to the necrotic border and also in small numbers at considerable distances in the surrounding cerebral tissue. In the earlier stages of development of the abscess most of these cells were present as gitter or pregitter types. In the present stage these types were in the minority, and many rod and irregularly shaped forms were present. Only at the margin of the necrotic zone was much phagocytosis observed.

Oligodendroglia: In this stage, as in the earlier phase of development of the abscess, oligodendrocytes were inconspicuous and did not seem to take an active part in the process.

Astroglia: The astrocytes were increased in number at some distance from the necrotic border. Occasionally, in the zones of greatest reaction, the gemästete forms of Nissl were seen. It is conceivable that these cells, either by nuclear division or by confluence of two or more cells, give rise to the giant cells, or *Monsterzellen*, which were often seen in this and later phases of abscess formation.

Nerve Cells: The nerve cells in the immediate vicinity of the reactive zone (fig. 4 *a*) had undergone complete dissolution. Nerve cells more remote from the reactive zone conformed to all degenerative stages previously described as chromatolysis, pyknosis and acute swelling.

Fibroblasts: It is the appearance of the fibroblasts which, more than any other single circumstance, serves to distinguish this phase in the formation of a cerebral abscess. In the foregoing observations relative to phase 1 fibroblasts were conspicuously rare. At this juncture these cells, although not as numerous as in later phases, were frequent enough to warrant attention. Particularly in figure 4 *b*, these cells can be seen most distinctly and in greatest concentration within the hyperemic zone which lies adjacent to the necrotic border. That they occupy in greatest numbers the region of hyperemia at once suggests their origin. Since the majority of the vessels in this region are of capillary dimensions and do not

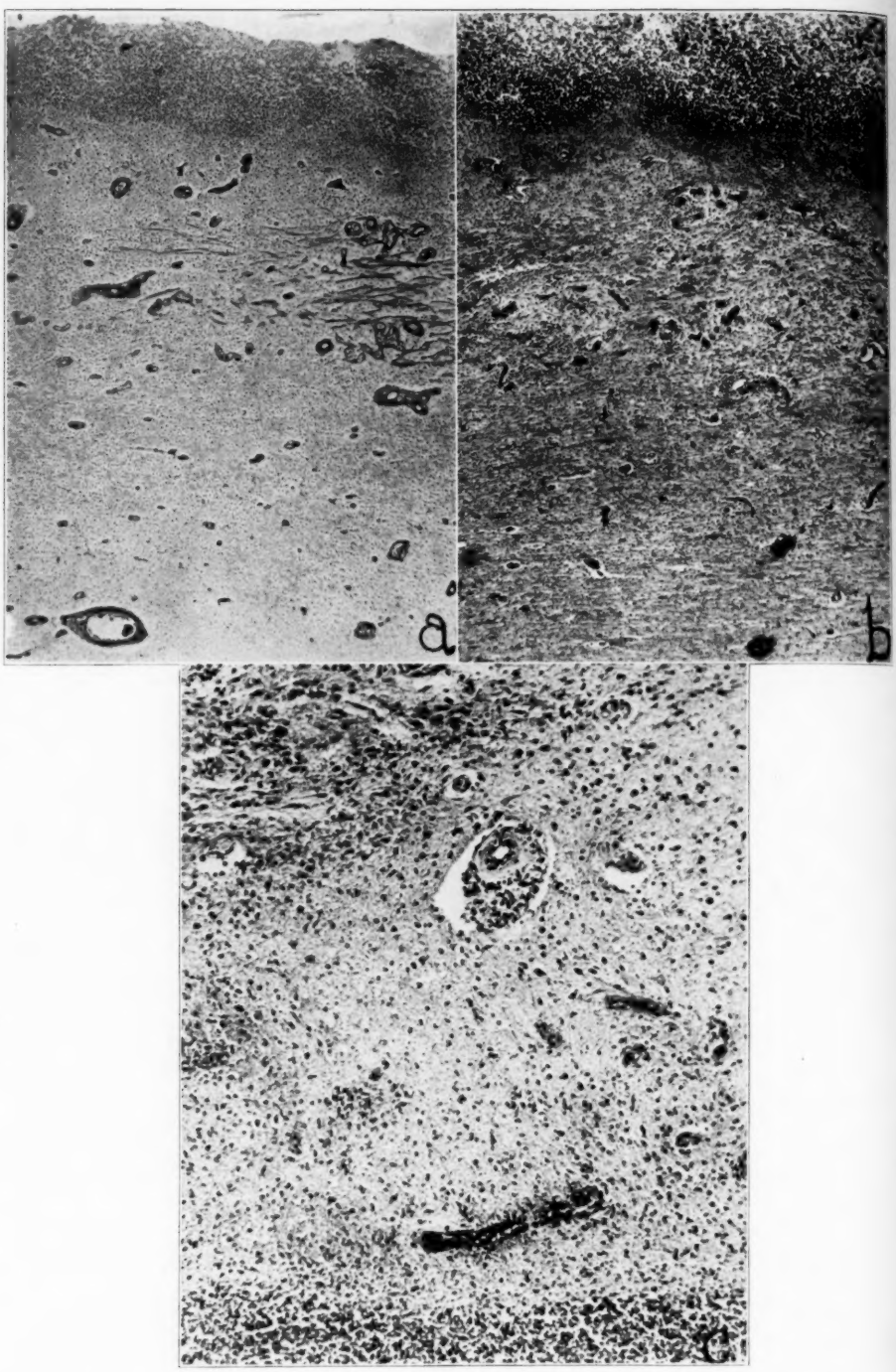

Fig. 5.—In *a* are shown the arrangement of the vessels in the hyperemic zone and their extreme perivascular cuffing (Perdrau stain; × 20); *b* illustrates phase III of the abscess, with four layers; (1) necrotic zone, (2) narrow band of amorphous debris, (3) zone of hyperemia and fibroblastic proliferation and (4) external zone of gliosis (hematoxylin and eosin; × 20), and *c* is a higher power of *b*, showing the inner three layers (hematoxylin and eosin; × 80). Note the extreme reaction of the large vessel in the upper central portion.

have recognizable adventitial structure in the form of fibrous tissue, one can scarcely conceive of their origin from previously existing fibroblasts in the immediate vicinity.

Hassin [51] demonstrated in the study of growing membranes that under such circumstances connective tissue is derived by transformation of the existing lymphocytes, which previously have migrated into the tissue. This was conceded by Globus and Horn.[41] Diamond and Bassoe,[52] on the other hand, attributed the existence of some of the fibroblasts to cells proliferating from the region near the walls of the blood vessels. Freeman,[53] in this connection, said: "Fixed tissue cells springing from the adventitia of blood vessels or from the meninges contribute to the formation of a wall of ever increasing density."

Relative to this, it is desirable to point out that nuclei in approximation to existing blood vessels and present in cells which morphologically are already fibroblastic are indistinguishable on this basis from the adjacent endothelial nuclei. This suggests the possibility of fibroblasts being derived immediately by transmutation of these endothelial cells. It is possible that these fibroblasts may be and are derived by all the modes which have been mentioned. Since any one of these observations or postulates is compatible with the fundamental concepts of histogenesis of connective tissue as related by Maximow,[54] they should constitute small cause for controversy.

The abscess at this stage of development is composed roughly of three main histologic portions: (1) the central portion, which is undergoing liquefaction and necrosis; (2) the adjacent layer of hyperemia and fibroblastic proliferation, and (3) the external, comparatively ill defined layer of early astrogliosis.

Phase III: Secondary Delimitation; Astrogliosis.—Examination of figure 5 *a, b* and *c* will show that the wall of the abscess in this phase is characterized merely by an exaggeration of most of the activities observed in phase II. These sections were obtained in the case of a boy aged 9 years who presented symptoms referable to the central nervous system the day after a severe injury to the orbit from a golf ball. Symptoms developed progressively for five weeks prior to operation, and the patient died nineteen days after drainage was instituted.

Hematogenous Elements: The activity and distribution of the leukocytes were much the same as in the previous stages. In this phase the perivascular spaces contained only the mononuclear types of leukocytes. Interposed between the central necrotic zone and the zone of hyperemia and fibroblastic proliferation was a darkly stained, narrow band (fig. 5 *b*) that represented products of disintegration

51. Hassin, G. B.: Histopathological Studies on Brain Abscess, M. Rec. **93**: 91-96 (Jan. 19) 1918.

52. Diamond, I. B., and Bassoe, P.: Abscess of the Brain: Report of Two Cases—One with the Clinical Picture of Epidemic Encephalitis and the Other with That of Tumor of the Brain, Arch. Neurol. & Psychiat. **19**:265-280 (Feb.) 1928.

53. Freeman, W.: Neuropathology: The Anatomical Foundation of Nervous Diseases, Philadelphia, W. B. Saunders Company, 1933, p. 123.

54. Maximow, A. A., and Bloom, W.: A Text-Book of Histology, Philadelphia, W. B. Saunders Company, 1930, pp. 48-71.

and condensation of cellular elements and tissue fluids. This was composed chiefly of fibrin, reticulin and a substance presumably derived from disintegrating blood, since it stained bluish by the Turnbull blue method.

Blood Vessels: Hyperemia, although still a conspicuous feature, was now overshadowed by the degree of perivascular proliferation present. It may be noted in figure 5 *a* and *b* that even the vessels nearest the zone of necrosis are possessed of perivascular spaces which are distended with cells. The existence of these perivascular spaces is of great importance in that it suggests that the vessels are not newly formed but existed previously and have merely become engorged. The distinction between such vessels and newly formed vessels will be discussed in detail in the description of the final phase.

Microglia: Gitter cells were still easily recognizable, scattered indiscriminately among the interstices of the fibrous tissue which was forming in the zone of hyperemia. Gitter cells as such were rarely seen in the necrotic center or in the adjacent border, although other forms of microglia cells were seen in profusion.

Oligodendrocytes: These cells maintained their previous inactivity throughout this phase, showing merely various degrees of degenerative change.

Astroglia: As the advent and activity of the microglia cells distinguished the first phase and the appearance of the fibroblasts distinguished the second, so the activity of the astrocytes is a distinguishing feature of the third phase. This activity of the astrocytes in the formation of the abscess seems to be the most irregular of the various steps of the process, both as to the time of its appearance and as to its extent. Usually, however, some alteration in the behavior of the astrocytes could be seen, rarely before, occasionally coincidentally with, but most often after the appearance of fibroblastic proliferation. As noted in figure 5 *b* and *c*, numerous astrocytes could be seen, appearing over the whole extent of the field, from the inner aspect of the fibrous layer, and intermingled with it, to a region considerably external to the fibrous zone. In the fibrous zone the glia fibers were freely intermingled with the processes of the fibroblasts and were indistinguishable from them by ordinary methods of staining. In the phase of activity particularly demonstrated by figure 5 *b* the extent of this gliosis was much greater than was ordinarily observed.

The astrocytes with which we are now concerned as being the distinguishing type of cell in this phase were first subdivided as an independent form in 1893 by Andriezen [55] and by Kölliker.[56] Shortly after there occurred a controversy as to whether these elements were independent units or a part of the syncytial background of the nervous structure. The latter view was held chiefly by the German school, in particular by Held,[57] who was supported by Hardesty.[58] In direct opposition were the now accepted views of the Spanish school of neuro-

55. Andriezen, W. L.: The Neuroglia Elements in the Human Brain, Brit. M. J. **2**:227-230 (July 29) 1893.

56. Kölliker, A., cited by Penfield, W.: Neuroglia: Normal and Pathological, in Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 2, pp. 421-480.

57. Held, H., cited by Penfield, W.: Neuroglia: Normal and Pathological, in Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 2, pp. 421-480.

58. Hardesty, I.: On the Development and Nature of Neuroglia, Am. J. Anat. **3**:229-268 (July) 1904.

histologists, notably Cajal,[59] del Rio-Hortega,[60] Achúcarro[61] and their pupils. The relationship of these cells by means of their so-called sucker feet to the parenchymal blood vessels has long been appreciated. Schaltenbrand and Bailey[32] expressed the opinion that cells do not pass this pial-glial membrane unless damage has occurred to the astrocytes. This condition of passage of cells through this barrier was encountered in all the previously described phases in which there occurred undoubted damage to the astrocytes that were related to the vessels nearest the lesion.

This "gliosis" which accompanies inflammatory lesions of the nervous system, a term commonly understood to mean only "astrogliosis," since the oligodendrocytes are inactive in the process, is a peculiar phenomenon. It is generally considered that it results from a chemotactic influence in the degenerating cerebral tissue rather than from the direct effect of the bacteria or their toxins on these cells. In speaking of inflammation, Greenfield[62] said: "It is largely a matter of speculation what is the precise nature of the disintegration product which produces this reaction. It is probable that many of the lipoids set free in the disintegration of myelin and of nerve cells have this power, but it is possible that it is possessed by some in a higher degree than by others . . . It is indeed generally accepted that cholesterin, either in its crystalline form or in some of its simpler combinations, may act as a chemical irritant which attracts wandering cells and causes proliferation of fixed cells."

It will have been observed from the previous descriptions and figures how these hypothetic concepts are satisfied by such lesions as we have considered. In the third phase we have noted the appearance of gliosis when destruction of elements has approached a maximum.

Mechanically or physically, the gliosis which we have considered is of small practical import as a reenforcement for the developing fibrous layer. In the study of sterile puncture wounds of the brain made by Wilson,[46] Essick[34] and Tschistowitsch,[63] the insignificance of this reaction as compared with that of the fibrous tissue was repeatedly emphasized. Under such circumstances Pfeiffer[64] asserted that glial reaction never occurred. Wilson[46] expressed the belief that the degree of filling in of such wounds depended on the amount of vascularity of the tissue, in the case of proliferation of connective tissue. Del Rio-Hortega and Penfield,[48] in the study of such sterile stab wounds, stated that proliferation of connective tissue depended on the amount of damaged tissue left in the wake of the puncturing instruments. They observed that when a core of connective tissue was not formed

59. Ramón y Cajal, S.: Contribución al conocimiento de la neuroglia del cerebro humano, Trab. d. lab. de invest. biol. Univ. de Madrid **11**:255-315, 1913.

60. del Rio-Hortega, P.: Estructura fibrilar del protoplasma neuróglico y origen de las gliofibrillas, Trab. d. lab. de invest. biol. Univ. de Madrid **14**:269-307, 1916.

61. Achúcarro, N.: De l'évolution de la névroglie et spécialement de ses relations avec l'appareil vasculaire, Trab. d. lab. de invest. biol. Univ. de Madrid **13**: 169-212, 1915.

62. Greenfield, J. G.: Inflammatory Cells in the Central Nervous System, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, pp. 1219-1238.

63. Tschistowitsch, T.: Ueber die Heilung aseptischer traumatischer Gehirnverletzungen, Beitr. z. path. Anat. u. z. allg. Path. **23**:321-350, 1898.

64. Pfeiffer, cited by Wilson.[46]

in such wounds there was no tendency for the radial arrangement of astrocytes. This, then, is suggestive that the previous advent of connective tissue in a wound influences more than a little the appearance and extent of gliosis.

Nerve Cells: At this stage the condition of nerve cells was much the same as that described in the previous phase.

Fibroblasts: We need merely mention that there was great exaggeration of the status of fibroblasts observed in the previous phase. Figure 5 *c* shows this reaction particularly well, and it is desired again to emphasize the occurrence of perivascular spaces surrounding even the vessels nearest the necrotic border.

An abscess at this stage is represented by four histologically recognizable layers; (1) the central zone of necrosis; (2) the adjacent narrow zone of condensed amorphous cellular debris; (3) the hyperemic zone which is fostering continued fibrous proliferation, and (4) the most external zone of gliosis.

Phase IV: Repair and Revascularization.—It is during the fourth phase that the most momentous change in the life cycle of an abscess occurs. Whereas heretofore the lesion has been ever advancing at the expense of cerebral tissue in a centrifugal direction, conditions are changed for the first time, and the progress of the lesion becomes centripetal, being directed toward the liquefied center in what appears to be an attempt to close the defect. The material illustrative of this phase was taken from 2 patients, shown in figure 6 *a, b* and *c*. The section illustrated in figure 6 *a* and *b* is from a patient who received a projectile wound of the head; the disease ran a course of forty-six days from the time of injury until death. Figure 6 *c* is a section from the abscess of a man aged 45 who exhibited symptoms referable to the central nervous system for seventy days before death. The first patient was not operated on; the second underwent multiple drainage operations. Thus, all the illustrations are of abscesses of considerably longer duration than those previously considered.

Hematogenous Elements: The activity of hematogenous elements was about the same as that described for the previous phase.

Blood Vessels: Examination of the blood vessels revealed noteworthy changes which distinguished this phase from those previously described. First, hyperemia, which was a constant feature of all previous phases, was no less apparent in this. On superficial examination (fig. 6 *c*) the vascular arrangement seemed to be analogous to its arrangement in previous stages, but this impression did not withstand closer scrutiny. First, the adjacent zone of what was previously the necrotic center was now not totally necrotic; the center was being invaded and replaced by papillomatous excrescences composed of every type of cellular element previously described, with the exception of polymorphonuclear leukocytes, which had disappeared from the picture, and of nerve cells which were not seen in the zone of reaction. Plainly visible within these proliferating excrescences were many newly formed blood vessels of small caliber. That these vessels were either new or proliferating immediately distinguished them from all vessels previously described. That they were newly formed seems to be supported by the fact that the position which they now occupied consisted, in previous sections, of only a conglomeration of debris and destroyed tissue. This structure is best shown in figure 6 *b*. The work of Pfeifer,[27] Lorente de Nó,[29] Cobb[28] and others showed adequacy of the existent vascular supply. Hence, the prominent hyperemia previously noted at

the margin of the advancing process was in all likelihood the result of dilatation of normally dormant, or alternately functioning, blood vessels which had existed before the advent of the lesion.

These newly formed vessels differed from such preexisting vessels not only in situation but also in structure. This structure will be of considerable importance to our interpretation of the development of this lesion. In the former phases the tendency throughout was toward continual expansion and enlargement of the lesion at the expense of cerebral tissue, which was destroyed by the lesion. In considering the vascular architecture of the previous phase, the occurrence of peri-

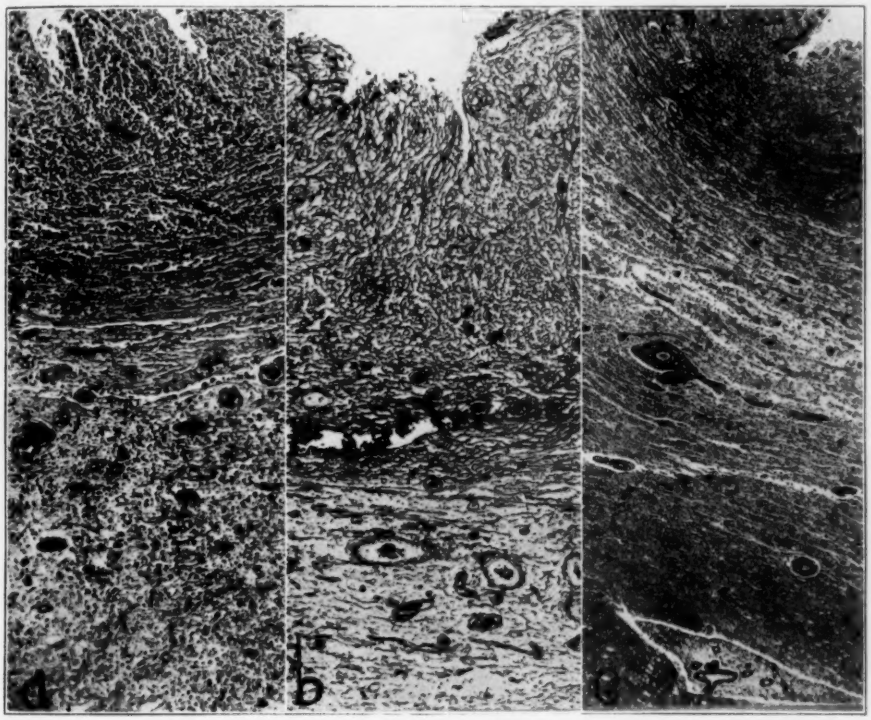

Fig. 6.—In *a* are shown four layers of an abscess of stage IV: (1) central necrotic zone, (2) revascularizing, granulomatous border, (3) zone of hyperemia and fibrosis and (4) external zone of gliosis (Van Gieson stain; × 60); *b* is an enlargement of the inner three layers, showing vessels of the granulomatous border devoid of perivascular spaces. Vessels in the zone of hyperemia and fibrosis at the lower part of the photomicrograph have perivascular spaces (Perdrau stain; × 18). In *c* is shown the continued existence of "perivasculitis" and turgidity of the Virchow-Robin spaces. The zone of gliosis is well shown in the lower left sector.

vascular spaces surrounding even the vessels adjacent to the advancing central lesion was stressed. This can be seen in figure 5 *c*. In contrast to this condition, one may see in figure 6 *b* that, although the vessels lying external to the fibrous

zone and most of the vessels lying within it possess perivascular spaces, the vessels which occupy the papillomatous nodules internal to the fibrous zone are not so constructed and appear to be devoid of such elaborations. The significance of this status of the vessels seems to be that now the advance of the lesion is halted and progress toward repair or obliteration of the lesion has begun. The first assumption is that in the proliferation of new blood vessels in the brain the anatomic refinement of the perivascular space either lags behind the essential process of forming a mesothelial tube or is neglected entirely. If this is an actuality, as it seems to be in this instance, the circumstance raises speculation as to its relation to the mode of spread, rupture and surgical management of such lesions.

Microglia: Interspersed within the fibrous layer and participating in the granulomatous repair of the necrotic center were to be seen all types of microglia cells previously described. Perhaps some were newly formed cells originating from those which had lingered in place from the beginning of activity, whereas others had merely been surrounded and enmeshed by the proliferating fibrous tissue.

Astroglia: At this point the arrangement and activity of the astroglia did not differ materially, except in degree, from what was observed in the previous stage.

Nerve Cells: The condition of nerve cells varied in sections that were two or more field diameters (low power) from the active lesion. Some cells showed severe degenerative changes, and some apparently were not abnormal. However, a recognizable increase in the degree of satellitosis seemed to be a constant feature in the last three phases.

Fibroblasts: At this point the degree of fibrosis was still considerably increased over that seen in phases II and III. This is best appreciated by studying figure 6 *a*. The fibrous zone, besides being greater in extent, was also much more compact. The peripheral portions had taken on a collagenous appearance (fig. 6 *a*). Excellent descriptions of abscesses approximately of the same histologic age are contained in the writings of Hassin [65] and Holmes; [66] both authors divided the zone of hyperemia and fibroblastic proliferation into its component parts, namely, the inner fibrous zone, the zone of hyperemia and the outer fibrous zone. Neither of these authors, however, emphasized the importance of the process of revascularization or any irregularities of vascular structure.

Summary.—In the foregoing descriptions we have endeavored to follow the course of formation of an abscess through the phases characterized by constant expansion and enlargement of the lesion at the expense of the cerebral tissue, at the same time noting the participation of the various reacting elements in proper sequence and degree. Up to this point the action has been predominantly centrifugal. At this point, however, it appears that for the first time the defense mechanism is becoming adequate and the action is reversed, so that now the activity of the cellular elements is directed centripetally and there seems to be a concerted attempt at repair of the lesion and obliteration of the defect.

An abscess in this advanced stage of formation may be described as composed of four layers: (1) the central necrotic core; (2) the revascu-

65. Hassin, G. B.: Histopathology of the Peripheral and Central Nervous Systems, Baltimore, William Wood & Company, 1933, pp. 233-236.

66. Holmes, J. B.: Multiple Abscesses of the Brain in Infancy, Arch. Int. Med. **17**:591-606 (May) 1916.

larizing, granulomatous border; (3) the zone of hyperemia and fibrosis, and (4) the external zone of gliosis.

Although it is not presumed that the ultimate stage of abscess formation is described here and that repair and obliteration of the lesion will follow, it is necessary to digress from the description temporarily in order to consider exceptions to the general mode of reactivity.

COMPLICATIONS OF THE LESION

Variations in the reaction during the formation of an abscess are of two main classes; first, the relatively frequent variations which differ from the previous descriptions only in the time of appearance and the degree of reaction shown by various groups of cells, and which we choose to term "regular variations;" second, and in contradistinction to the first, those variations of development which constitute such a great departure from the normal mode of development that they properly must be termed "complications."

Of the regular variations it may be said briefly that in many cases there is noted a certain tardiness in appearance or modification of the degree of reactivity on the part of certain elements or systems of elements. This dyssynchronism in appearance and relationships of the various elements usually does not continue through the entire cycle of evolution but appears only as an irregularity of one or more phases, so that ultimately the final similarity in appearance of the abscess is attained and the variation is of no real importance.

The irregular variations are of greater importance, and such departures from the normal constitute "complications." These types of evolution will be considered briefly more or less in the order of their appearance in the cycle of abscess formation.

Necrotic Cerebritis.—This condition, a variation of the initial phase of formation of an abscess termed by Bagley [67] "suppurative encephalitis," can hardly be called a true complication of an abscess, for usually it is seen before any semblance of the formation of an abscess is recognizable. This lesion consists of multiple, often connected, rapidly coalescing zones of focal necrosis without delimitation, which spread rapidly through and destroy the cerebral tissue. Such lesions, when examined at necropsy, do not show delimitation, either because of an imbalance between the virulence of the organism and the immunologic factors involved or because the issue has been fatal, due to meningitis or disturbed intracranial hydrodynamics, before the defensive reaction has had time to occur. Such lesions are well exemplified by the photomicrographic illustrations of phase I, which differ from these lesions only in extent and outcome.

Meningitis.—This complication is probably responsible for more deaths from abscess of the brain than any other single condition. It constitutes a continual

67. Bagley, C., Jr.: Brain Abscess with Pathological Observations, Surg., Gynec. & Obst. **38**:1-13 (Jan.) 1924.

source of apprehension which besets all who would attempt operative treatment of cerebral abscess. Occasionally abscesses are seen at necropsy which, although apparently well circumscribed, have produced death by this means. In such instances one is forced to presume that infection has been transmitted from the abscess itself by way of the vascular system. Abscesses enlarging so as to approach the pial or ependymal surfaces of the brain may give rise to meningitis, although in this instance it is more usual to observe that the enlarging lesion, which is somewhat circumscribed, produces adhesive arachnoiditis, which has the effect of excluding the subarachnoid space and thereby safeguards the organism from meningitis. However, as will later be considered, abscesses may rupture during the course of operative procedures in such a manner that the subarachnoid space is contaminated and meningitis results.

Diverticulation.—Although the term "diverticulation" may be found objectionable on grounds of definition, it seems to distinguish this type of complication from two other types. This complication usually is seen at the stage of primary delimitation and is characterized by irregular extension of the abscess. Diverticulation differs from the irregular spread or extension of the primary focus which is associated with "necrotic cerebritis" in that it occurs later in the evolutionary cycle, after a slight degree of delimitation has occurred. Likewise, this complication differs from rupture in that an abscess conceivably cannot rupture until it has become definitely restricted by a limiting membrane. Diverticulation, then, represents a form of extension of the abscess after restrictive reaction has begun, but before actual delimitation has occurred.

Such an instance is well illustrated in figure 7. Here, there is slight and recognizable reaction in the marginal tissue of this dumb-bell-shaped lesion, and close microscopic scrutiny reveals that the two portions of the abscess are of slightly, but definitely, different ages, the lesion on the left being older than that on the right. In this figure the apparent trabeculae that extend into the margin of the lesion on the left are cords of gitter cells loaded with fat, cells and other debris. These cells are less numerous and not so well organized in the lesion on the right. Since the illustration was taken from the same case as that illustrated by figures 2 and 3, it serves also to demonstrate the occurrence of multiple abscesses of different ages in the same patient.

Since the general tendency in the formation of an abscess is toward the assumption of a spheroid one may wonder concerning this phenomenon of diverticulation. Probably it results from the unequal progression of the limiting process in some portions of the restricting wall while this is in the process of formation, so that the pressure that results from liquefaction of the center is relieved by extrusion of the contents gradually through the weakest point. This may result solely from alteration of the balance between the pressure, on the one hand, and the factors of resistance of the tissue, on the other, as considered physically, or, as is also likely, it may be due to involvement of the vascular tree in such a manner that an adjacent zone of brain tissue becomes infarcted and hence offers less resistance to the advancing lesion.

At this point it is important to mention another interesting physical attribute of abscesses. Although abscesses of the brain may result from almost any, if not all, pyogenic organisms and may be of almost any size, two noteworthy observations were made. Whereas abscesses 2 cm. or more in diameter may be seen in all stages of delimitation, it is rare to observe a smaller abscess which has progressed

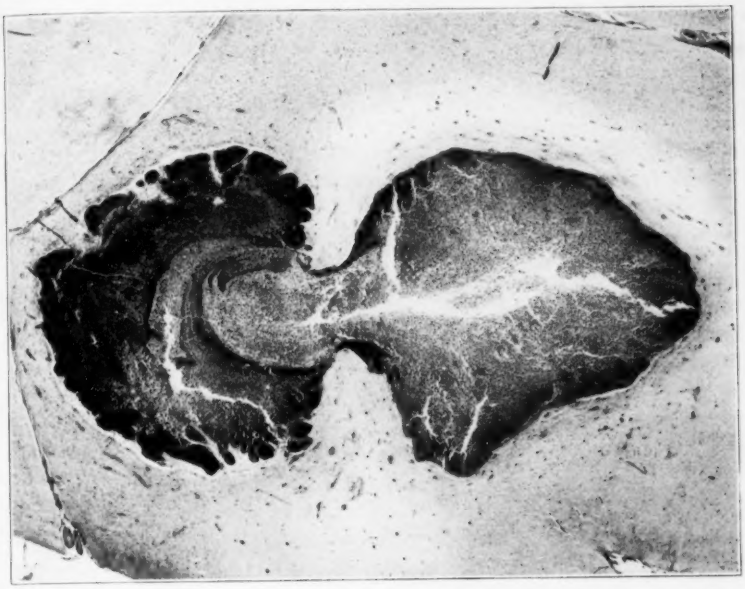

Fig. 7.—"Diverticulation." The abscess on the left is microscopically older than that on the right. For enlargement of the margin, see figure 3. Hematoxylin and eosin; × 8.

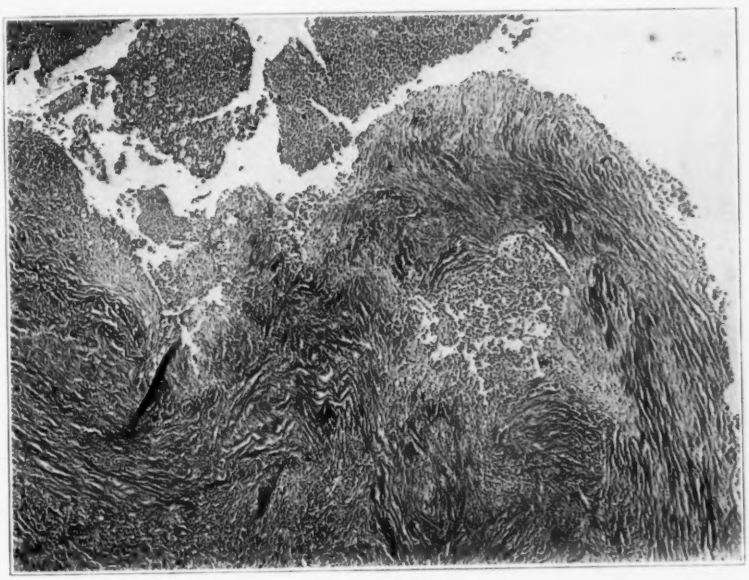

Fig. 8.—Rupture of the wall of a well formed abscess, with the formation of a secondary abscess. The two lesions are connected. Perdrau stain; × 60.

beyond the delimitation corresponding with the second phase. It appears that an abscess usually must attain a certain size before encapsulation can be more than rudimentary.

Rupture.—Rupture may occur in three conceivable ways, namely, by spontaneity, by traumatism or by surgical intervention. Although this complication occurs late in the evolution of the lesion and is admittedly serious, it does not necessarily result fatally, as delimitation may occur after the catastrophe. This is illustrated in case 30 reported by Macewen,[3] in which he discovered a well circumscribed primary abscess suspended in the pus that had been formed by a well delimited surrounding secondary abscess. Figure 8 illustrates a process of this type. A microscopic abscess can be seen within the wall of the already well formed, well circumscribed abscess. One may visualize easily how this condition might become aggravated by the passage of time until the conditions described by Macewen were approximated. The section shown in figure 8 was obtained from a patient who had suffered severe trauma of the head with fracture and subsequent cranial osteomyelitis. Hemiparesis and aphasia had suddenly developed only ten days prior to death. The abscess appears much older than the acute history indicates.

Hemorrhage.—Hemorrhage into the cavity of an abscess, if one is led to make any analogy between abscess and neoplasm, may be considered a possible complication. In the study of this series of cases such a lesion was not encountered, nor were descriptions found in the literature. If such a complication exists it must be rare. We have emphasized the occurrence of small hemorrhages in the walls of developing abscesses. One may wonder why occasionally the liquid center of the abscess is not filled with extravasated blood. However, when one considers that after the perivascular hemorrhage that is observed routinely in the developing lesions obliterative endarteritis and endophlebitis occur, the reason may be evident. Again, the pressure that exists in the necrotic center may be a factor, and it is possible that the internal pressure of the abscess is greater than the blood pressure in the small adjacent vessels. This is borne out by the common experience of seeing pus rush out of an abscess with considerable force when a cannula is introduced; yet the absence of hemorrhage may bear some relationship to the structural arrangements of the adjacent vessels.

COMMENT

What, then, are the pathologic conclusions concerning such an abscess as that described in the fourth phase? Is one to assume that such a lesion will heal by obliteration of the cavity? Such a termination of a cerebral abscess must be rare indeed. Both Globus and Horn [41] and Macewen [3] have raised this question. Globus and Horn cited a case in which this result had almost been achieved, but they did not go so far as to say that abscesses do heal spontaneously. Macewen cited a case in which it was possible and stated that he thought such a result might obtain in small abscesses. This is, of course, contrary to experience in this study. As has been mentioned, small abscesses rarely were observed to exceed the state of development represented by phase II. However, spontaneous healing of small abscesses probably occurs in

some instances, in which cases the lesion, of course, is not subjected to close pathologic scrutiny. In the present study such spontaneously healed abscesses, large or small, were not encountered.

Spontaneous evacuation of an abscess is, by circumstance, a remote possibility. Situated as it is within the rigid confines of the skull, evacuation to the exterior is scarcely a practical consideration. However, such cases as that reported by Macewen in which the abscess evacuated itself through the mastoid tract and the one reported by Drummond [68] in which the abscess pointed externally above the zygoma serve to illustrate that such a termination may occur. Internal evacuation, or rupture, of an abscess into the subarachnoid space or into the ventricles is relatively frequent and usually results in fatal meningitis or ependymitis.

It is not within the scope of this study to consider any clinical features of cerebral abscess. These aspects are competently outlined in the writings of Kennedy,[69] Lillie,[70] Benedict,[71] Woltman [72] and Fremont-Smith,[73] all of whom discussed the correlation of the symptomatology with the underlying pathologic process. Likewise, the relation of the stage of pathologic development to surgical management has been commented on adequately by Adson,[74] Adson and Craig,[75] Coleman,[76] Dandy,[77] Dowman,[78] Elsberg,[79] Lemaitre,[80] Linck [81] and King.[82]

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68. Drummond, H.: Abscess of the Brain That Pointed Externally, Brit. M. J. **1**:995-996 (June 7) 1924.

69. Kennedy, F.: Diagnosis of Abscess of the Brain, Arch. Neurol. & Psychiat. **22**:627-629 (Sept.) 1929.

70. Lillie, W. I.: The Clinical Significance of Choked Discs Produced by Abscess of the Brain, Surg., Gynec. & Obst. **47**:405-406 (Sept.) 1928.

71. Benedict, W. L.: Brain Abscess from the Standpoint of the Ophthalmologist, Laryngoscope **40**:325-335 (May) 1930.

72. Woltman, H. W.: Spinal Fluid Cell Count and Encapsulation of Brain Abscess: An Attempt to Correlate These Factors, and Determine the Optimal Time for Drainage, J. A. M. A. **100**:720-722 (March 11) 1933.

73. Fremont-Smith, F.: Pathogenesis of the Changes in the Cerebrospinal Fluid in Meningitis, Arch. Neurol. & Psychiat. **28**:778-788 (Oct.) 1932.

74. Adson, A. W.: The Surgical Treatment of Brain Abscess, J. A. M. A. **75**:532-536 (Aug 21) 1920.

75. Adson, A. W., and Craig, W. M.: The Surgical Management of Brain Abscess, Ann. Surg. **101**:7-26 (Jan.) 1935.

76. Coleman, C. C.: The Treatment of Abscess of the Brain, Arch. Surg. **18**: 100-116 (Jan.) 1929.

77. Dandy, W. E.: Treatment of Chronic Abscess of the Brain by Tapping: Preliminary Note, J A. M. A. **87**:1477-1478 (Oct. 30) 1926.

78. Dowman, C. E.: The Treatment of Brain Abscess by the Induction of Protective Adhesions Between the Brain Cortex and the Dura Before the Establishment of Drainage, Arch. Surg. **6**:747-754 (May) 1923.

(Footnotes continued on next page)

It should be mentioned, however, that the recent use of sulfanilamide, as reported by Bucy [83] and others, may influence favorably the preoperative care and the postoperative management of this condition. This new weapon, coupled with the method of tapping advocated by Dandy, may prove fruitful. It is to be emphasized that, according to the interpretation of this study, there is a stage in the development of an abscess in which the abscess might heal, not spontaneously, but if aided by surgical reduction of its internal pressure by tapping, the natural reparative process being thus allowed to go forward to final obliteration of the necrotic center, as a continuation of the process described in the fourth and final phase of its cycle.

However, it is important from the pathologic point of view to ascertain, if possible, whether there is any direct correlation between the stage of pathologic development of an abscess and its age; undoubtedly, it requires time for the development of an abscess, and it seems logical that, for abscesses of similar nature in similar situations and under similar circumstances, the same periods should be approximated, at least roughly, for the attainment of comparable pathologic pictures. Regardless of how true this may be, it at once becomes extremely difficult, if not impossible, to compare these two factors, for there is no method of arriving at the age of an abscess other than by consideration of its symptomatology, except in cases in which the abscess results from traumatism. As an example of this problem, one may consider photographs *a* and *c* in figure 6, which illustrate abscesses in comparable stages of development and therefore, presumably, of comparable pathologic age. It seems that the temporal age of the second abscess is at least twice that of the first, judging from the complete clinical history. This is probably not true. Therefore, it seems impossible, with the material at hand, to correlate definitely and dependably these two factors.

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79. Elsberg, C. A.: The Technic of Operations for Abscess of the Brain, Arch. Otolaryng. **1**:14-25 (Jan.) 1925.

80. Lemaitre, F.: Walling Off the Subarachnoid Spaces: Its Application to the Treatment of Cerebral and Cerebellar Abscess of Otitic Origin, and, in a General Way, to the Surgery of the Brain, Ann. Otol., Rhin. & Laryng. **29**:1-32 (March) 1920.

81. Linck: Beitrag zur Klinik und Pathologie der Hirnabszesse, Deutsche Ztschr. f. Chir. **166**:65-105 (Sept.) 1921.

82. King, J. E. J.: The Treatment of Brain Abscess by Unroofing and Temporary Herniation of Abscess Cavity with the Avoidance of Usual Drainage Methods, with Notes on the Management of Hernia Cerebri in General, Surg., Gynec. & Obst. **39**:554-568 (Nov.) 1924.

83. Bucy, P. C.: Sulfanilamide in the Treatment of Brain Abscess and Prevention of Meningitis, J. A. M. A. **111**:1639-1641 (Oct. 29) 1938.

From a purely pathologic point of view, it has been the time-honored custom to estimate the age of an abscess by considering the width of the fibrous lamina which restricts it. Likewise, it has been considered that fibrous tissue in itself bespeaks the age of an abscess, which is true; still, this gives little information as to the actual status of the abscess except to enable one to say that one abscess appears young, another middle aged and another very old; thus one may compare them relatively without attempting to compare their ages by days, weeks or months. It has been emphasized that the chronologic age of an abscess is not as important as its stage of development. We have seen 2 examples of abscess, circumscribed by fibrous tissue, which were pathologically considered as a relatively young and an advancing lesion, respectively. It is here suggested that it is more accurate to judge the pathologic status of an abscess by consideration of its activity, the best clue to which lies in the arrangement and activity of its associated vasculature. From these criteria it is believed that the advancement or regression of an abscess can be determined. Likewise, hemorrhage is an important consideration in the microscopic picture of an abscess, for it is believed that as long as hemorrhage forms an important feature of the picture the abscess is advancing; consequently, it is pathologically young.

The terms "capsule" and "encapsulation" have purposely been avoided as much as possible in this presentation. Although these terms cannot be objected to on the basis of definition, their connotation is likely to lead to overestimation of the physical attributes of the membrane that restricts the usual well developed abscess. Abstract consideration of such a restricting membrane reveals in the case of the more highly evolved ones, as illustrated in phase IV, that the wall is composed of a loosely woven tissue the overall linear dimensions of which are somewhat greater than 1 mm., and usually not more than 2 mm., in thickness. The wall is composed of loosely bound fibroblasts, reenforced by intertwining vessels of the smaller caliber, and externally is strengthened by a thin, compressed lamina of glial reaction. Undoubtedly, walls older and thicker than this do occur, but this represents fairly the composition of the average wall of an abscess which ultimately requires surgical intervention.

SUMMARY

In the foregoing description we have outlined the course of evolution of cerebral abscess from its microscopic inception through various arbitrary stages to this mature conclusion; we have commented also on the irregularities of development frequently seen and the complications which the lesion may suffer in the course of its life cycle. Suggestions also have been made as to which of the microscopic structures and processes involved offer the most accurate estimation of the status of the process as a whole.

A ROENTGENOGRAPHIC SIGN IN CASES OF TUBEROUS SCLEROSIS OF BRAIN (MULTIPLE "BRAIN STONES")

PAUL I. YAKOVLEV, M.D.
WAVERLEY, MASS.
AND
WILLIAM CORWIN, M.D.
WALTHAM, MASS.

The cardinal clinical symptoms of tuberous sclerosis of the brain, also known as Bourneville's disease, are: epilepsy; mental deficiency of varying degree, and the so-called naevus multiplex of Pringle, consisting of multiple wartlike nodules distributed symmetrically in a butterfly fashion over the bridge of the nose and the cheeks and chin. For a detailed account of the symptomatology and pathology of the disease, the reader is referred to earlier publications.[1] The condition is often familial and sometimes hereditary, and belongs to the group of ectodermal dysplasias (congenital ectodermoses).[1] The disease is more frequent than is generally recognized. When the facial naevus multiplex of Pringle is present in the complete classic form of the disease, the diagnosis is almost self evident. On the other hand, when the nevus is not present and the epilepsy is the only clinical sign, the specific pathologic lesions underlying the disease may easily be overlooked.[2] This eventuality explains the apparent rarity of the condition. It is therefore worth while to consider the signs and manifestations of the disease, other than cutaneous nevi, which permit one to recognize, or at least to suspect, tuberous sclerosis of the brain in its clinically incomplete or abortive forms. The roentgenographic signs may espe-

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Read at a meeting of the Boston Society of Psychiatry and Neurology, April 20, 1939.

From the Walter E. Fernald State School and the Metropolitan State Hospital, Waltham, Mass.

1. (*a*) Yakovlev, P. I., and Guthrie, R. H.: Congenital Ectodermoses (Neurocutaneous Syndromes) in Epileptic Patients, Arch. Neurol. & Psychiat. **26**:1145 (Dec.) 1931. (*b*) Yakovlev, P. I.: Neoplastic Malformations Affecting with Predilection the Skin, Retina and Nervous System: Congenital Ectodermoses, in Blumer, G., and Lane, C. G.: The Practitioners Library of Medicine and Surgery, New York, D. Appleton-Century Company, Inc., 1936, vol. 9, chap. 27.

2. Yakovlev, P. I.: Congenital Morphologic Abnormalities of the Brain in a Case of Abortive Tuberous Sclerosis, Arch. Neurol. & Psychiat. **41**:119 (Jan.) 1939.

cially be useful. Gottlieb and Lavine [3] reported a case of tuberous sclerosis in an epileptic woman aged 23, and demonstrated the roentgenographic changes in the bones. In the skull the changes consisted of thickening, osteoporosis and mottling of the bones. In the extremities there were periosteal thickenings, and the metacarpal bones and their associated phalanges showed "a few round areas of increased rarefaction, suggesting cysts." The laboratory findings in this case were all noncontributory. The calcium and phosphorus contents of the blood were normal.

Berkwitz and Rigler [4] reported the case of a 2 year old epileptic girl with cleft palate and a family history of epilepsy, but without facial nevus. The nevus of the face in cases of tuberous sclerosis often does not develop until after puberty. In this child pneumoencephalograms revealed multiple tumor-like, dense areas projecting into the lateral ventricle. On this evidence the authors diagnosed the condition as tuberous sclerosis. The encephalographic findings reported by them may perhaps be legitimately accepted as diagnostic of tuberous sclerosis, since the multiple spongioblastic tumors, so-called candle gutterings, in the lateral ventricles are a characteristic cerebral abnormality in this condition. It is somewhat disturbing to note that in the illustrations in their paper the dense areas project into the ventricle from its roof and posterior wall. As a rule these tumors are found in the floor of the lateral ventricle, and characteristically in the striothalamic sulcus [2] rather than in the roof.

The two observations just cited show that tuberous sclerosis may have roentgenologic signs, namely, the osteoporotic and cystic changes in the distal bones of the extremities, described by Gottlieb and Lavine, and the characteristic multiple irregularities in the contour of the lateral ventricles, shown by Berkwitz and Rigler, which should be found more frequently in the floor of the ventricles than in the roof.

We wish to draw attention to a third roentgenologic manifestation of tuberous sclerosis, which we believe to be of greater diagnostic significance than the other two, namely, the multiple disseminated areas of intracerebral subcortical calcification—the multiple "brain stones."

REPORT OF A CASE

History.—S. W., a man aged 26, at 22 years of age was admitted to a state hospital for mental diseases with a diagnosis of "psychosis with convulsive disorders—idiopathic epilepsy." The family history traced on the paternal side

3. Gottlieb, J. S., and Lavine, G. R.: Tuberous Sclerosis with Unusual Lesions of the Bones, Arch. Neurol. & Psychiat. **33**:379 (Feb.) 1935.

4. Berkwitz, N. J., and Rigler, L. G.: Tuberous Sclerosis Diagnosed with Cerebral Pneumography, Arch. Neurol. & Psychiat. **34**:833 (Oct.) 1935.

through three generations showed dominant "epileptoid" personality traits in the grandmother, her cousin, the father, 2 aunts and 1 cousin, but not frank epilepsy. On the maternal side distinct "schizoid" heredity was found. The mother died in a hospital for mental disease at the age of 34, of a condition diagnosed as "dementia praecox—catatonic." Of 2 living sisters, 1 was said to have "fainting spells"; both were reported to be emotionally unstable.

In the patient's personal history there was nothing significant except that since early childhood he had suffered from epilepsy. At about the time when the recurrent epileptic seizures had begun his family noticed an acne-like "eruption" on his face, which had persisted since. The "eruption" was always attributed by the family to his "spells," and no further attention was paid to it. He was always considered a "nervous" child, but by the time he reached maturity the changes in personality and abnormalities of conduct so often associated with chronic epilepsy rendered him socially dangerous and necessitated his commitment.

Fig. 1.—Photograph of S. W., with a facial naevus multiplex of Pringle. Note the butterfly distribution of multiple nodules over the bridge of the nose, cheeks and chin.

Examination.—The patient was poorly developed, puny and immature appearing, and had epileptic seizures on the average of about once a month. He was emotionally unstable, overreligious, overscrupulous, ingratiating, impulsive and explosively irritable and was given to unpredictable swings of depressive mood, when he became suicidal. He showed evidence of deterioration. The skin of the face bore a typical symmetric naevus multiplex of Pringle, with a butterfly distribution over both cheeks and the nose and chin (fig. 1).

General medical, neurologic and laboratory examinations revealed no significant abnormalities. The value for calcium in the blood was 10.01 mg. per hundred cubic centimeters, for phosphorus 3.71 mg. and for phosphatase 3.62 mg. Lumbar puncture showed normal pressure (180 mm. of water) and normal dynamics, with a high Ayala's quotient (12.2). Examination of the cerebrospinal fluid showed a value for total protein of 20 mg. per hundred cubic centimeters, for sugar of

91 mg. and for chlorides of 732 mg.; there were no cells, and the Wassermann reaction was negative.

Roentgenographic Examination.—The findings in the roentgenograms and pneumoencephalograms, on the contrary, were significant. They revealed no definite signs of ventricular tumor and showed only slight dilatation of the occipital horns of the lateral ventricles. The cranial vault was rather thin. In the distal phalanges of the fingers there were a few cystlike areas of rarefaction. However, the roentgenogram and the encephalogram both showed numerous opacities scat-

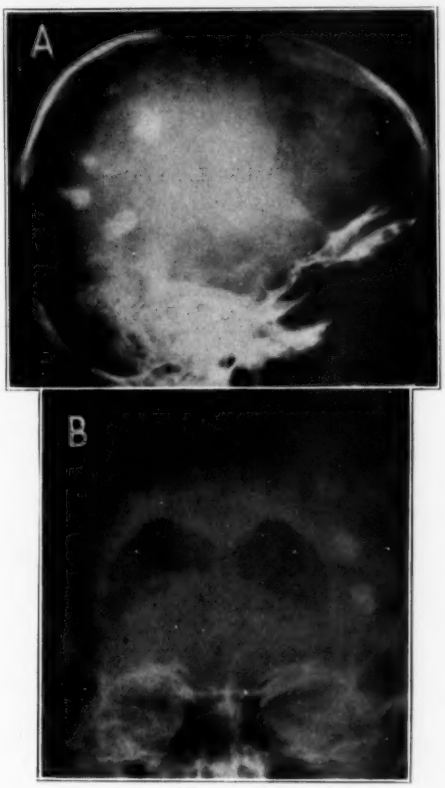

Fig. 2—*A*, roentgenogram of S. W. Note the multiple cotton ball-like opacities disseminated in the substance of the occipital and parietal lobes. *B*, pneumoencephalogram of S. W. Note the moderately dilated lateral ventricles and multiple intracerebral opacities.

tered throughout the substance of the parietal and occipital lobes of the brain (fig. 2 *A* and *B*). Stereoscopic plates showed clearly that the areas of increased density disseminated in the brain were characteristically distributed, not near the ventricles or in the cortex, but in the white matter, some distance under the cortex.

These findings led us to make a roentgenologic survey of 5 other cases of tuberous sclerosis. In addition to thickening of the cranial

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vault, 4 patients showed in varying degrees dissemination in the brain of the multiple areas of opacity. A roentgenogram in 1 of these cases, that of an idiotic epileptic woman aged 26 with an unusually coarse facial nevus of Pringle, is reproduced here (fig. 3).

Significantly, all the patients who showed the intracerebral opacities in roentgenograms were in the older group (past puberty), whereas 1 patient in whom no opacities were found was a girl about 7 years of age.

COMMENT

It is consistent with the histologic and metabolic peculiarities of the tuberosclerotic nests in the cortex and of the spongioblastic tumors in the ventricles that many of them should eventually become opaque to roentgen rays. The pronounced tendency to deposition of calcium is indeed a characteristic trait of both varieties of tuberosclerotic lesions.

Fig. 3.—Roentgenogram of an idiotic-epileptic woman aged 36 with Pringle's nevus of the face. Note a large cotton ball-like intracerebral opacity above the sphenoid bone, with several others faintly visible nearby and in the occipital lobe. Note also the thickening and fuzzy appearance of the cranial vault.

In the ventricular spongioblastic tumors the calcification begins, and is always more dense, in the center of the tumor, where calcareous granules, forming clusters, are usually heaped around proliferated, calcified, hyalinized and degenerated capillaries (fig. 4).

In tuberosclerotic nodules in the cortex, the relation of calcareous precipitates in the nerve tissue to the nodule is different. Here the calcification tends to occur not in the center of the nodule but in the periphery of the subcortical softening facing the white matter, that is, under the cortex in the depth of the convolutions (fig. 5).

The heterotopic nests of monster nerve cells and glia, forming nodules, may occur not only in the convolutions but also deep in the white matter of the centrum semiovale.

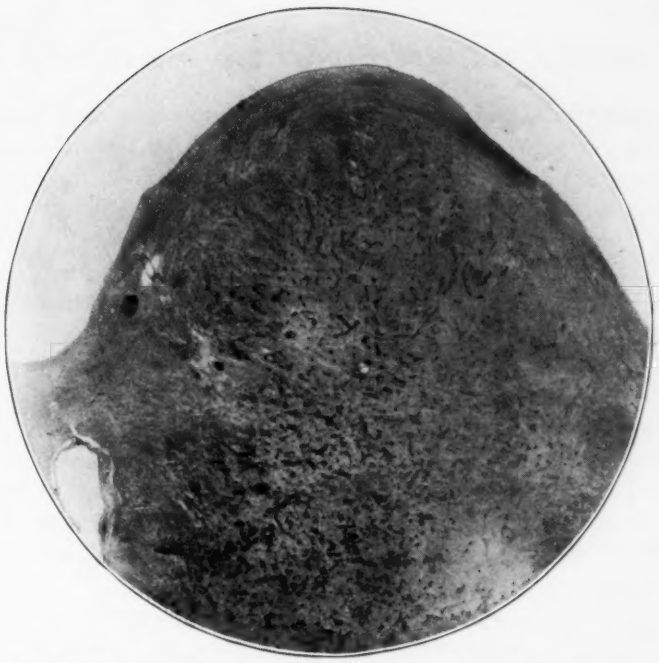

Fig. 4.—Low power photomicrograph (Zeiss objective no. 3) of one of the multiple tumors in the floor of the lateral ventricle in a case of tuberous sclerosis. Note the calcification of the capillaries and the calcium granules in the center of the tumor.

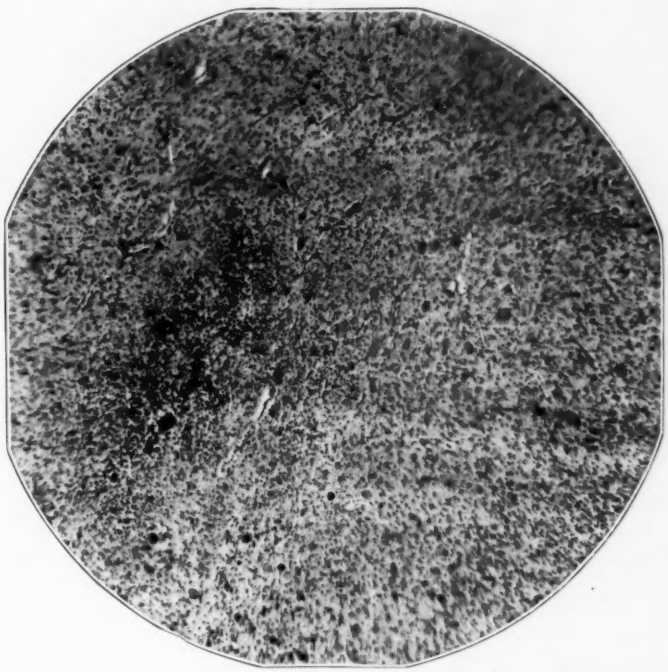

Fig. 5.—Low power photomicrograph (Zeiss objective no. 6) showing deposition of calcium granules in the white matter underlying the tuberosclerotic nodule in the cortex. Numerous large glia cells can be seen scattered through the field.

The precipitation of calcium in the nodules is a secondary process developing as a sign of degenerative changes in the congenital neoplastic lesion. At first slight and invisible, the precipitation in the course of years gradually grows denser and eventually becomes sufficiently opaque to roentgen rays to appear clearly evident on the plates. Clinically, this is an important roentgenologic sign in cases of tuberous sclerosis, for it is directly related to and is revelatory of specific cerebral pathologic changes underlying the condition.

It is noteworthy that the tendency to calcification of the brain substance is a feature of tuberous sclerosis which it shares with another characteristic congenital neurocutaneous syndrome, namely, trigeminocerebral angiomatosis. The roentgenographic picture of the calcification in the two conditions is, however, quite different. In tuberous sclerosis the opacities resemble "cotton balls" with fuzzy periphery, whereas in angiomatosis the calcareous depositions in the cortex acquire a garland-like appearance, not unlike that of ribbon candy.

There exists another variety of intracerebral calcification demonstrable roentgenographically and frequently associated with mental deficiency, epilepsy and a neuropathic family history. The intracerebral calcification as shown on roentgenograms in this condition is characterized by a diffuse, massive and remarkably symmetric deposition of calcium, particularly in the region of the basal ganglia.[5] The roentgenographic image obtained is therefore different from that of multiple, discrete and scattered (nonsymmetric) areas of calcification in tuberous sclerosis.

DISCUSSION

DR. TRACY J. PUTNAM: I wish to ask Dr. Yakovlev if anything is known of the pathologic process underlying rarefaction of bone tissue. Also, are these areas of calcification in the brain areas of degeneration such as one might see with small infarcts, or are they specifically related to the neoplastic process of tuberous sclerosis?

DR. PAUL I. YAKOVLEV, Waverley, Mass.: Little is known about the changes in the bone in tuberous sclerosis. I may point, however, to the similarity of the areas of rarefaction in the bones to the subperiosteal cysts seen occasionally in cases of Recklinghausen's neurofibromatosis. The latter apparently differ in origin from cystic osteoporosis associated with parathyroid hypercalcemia—a condition also sometimes referred to as Recklinghausen's disease. In neurofibromatosis the subperiosteal cysts seem to be related to a local neoplastic process—periosteal

5. Fritzsche, R.: Eine familiär auftretende Form von Oligophrenie mit röntgenologisch nachweisbaren symmetrischen Kalkablagerungen im Gehirn, besonders in den Stammganglien, Schweiz. Arch. f. Neurol. u. Psychiat. **35**:1, 1935. Kasanin, J., and Crank, R. P.: A Case of Extensive Calcification in the Brain: Selective Calcification of the Finer Cerebral Blood Vessels, Arch. Neurol. & Psychiat. **34**:164 (July) 1935. Eaton, L. M.; Camp, J. D., and Love, J. G.: Symmetric Cerebral Calcification, Particularly of the Basal Ganglia, Demonstrable Roentgenographically: Calcification of the Finer Cerebral Blood Vessels, ibid. **41**:921 (May) 1939.

schwannomas—forming cysts in the bone. Many analogies between tuberous sclerosis and neurofibromatosis lead one to think that the bone changes in the two conditions may also be similar.

The areas of calcification in the brain are areas of degenerative softening in the neoplastic tissue. Anoxemia is a common factor in the softening following infarction and in the softening within the tuberosclerotic nodule. However, in infarction the anoxemia is secondary to shutting off of the blood supply, while in the tuberosclerotic nodule it is the result of primary deficiency of intracellular metabolism in the neoplastic tissue. While the origin of degeneration in the two instances is different, the end result—calcification—is the same.

ACUTE ANTERIOR POLIOMYELITIS (HEINE-MEDIN DISEASE?) WITH UNUSUAL CEREBRAL MANIFESTATIONS

CLINICAL AND PATHOLOGIC REPORT OF A CASE

RICHARD B. RICHTER, M.D.
CHICAGO

Involvement of the brain in acute poliomyelitis is, as is well known, a commonplace observation even when it has not been indicated clinically. Conversely, the gray matter of the cord has been found to be implicated in epidemic encephalitis sufficiently often to warrant the recognition of a poliomyelitic form of this disease. The cerebral complications encountered in the present case of poliomyelitis, however, were so extraordinary in kind and degree, both clinically and pathologically, that they are herewith reported.

REPORT OF CASE

Clinical History.—C. J., a schoolboy aged 14, was admitted to the Albert Merritt Billings Hospital, to the service of Dr. George F. Dick, on Sept. 9, 1937, because of pain and weakness of the arms and legs. He had been well until five days before, when he had a severe headache which persisted. Mild gastrointestinal symptoms had been present during the next few days, and on the day before entrance he began to complain of soreness of the muscles of his arms and legs and of weakness of his right arm.

Examination.—The temperature on admission was 38.8 C. (101.8 F.), the pulse rate 110 and the respiratory rate 22. There was nothing remarkable in the results of general physical examination at this time. On neurologic examination he responded to questions and cooperated in the procedures, but there was some clouding of the sensorium. There was marked rigidity of the neck, and attempts to flex it passively were extremely painful. Respiration was shallow, rapid and labored, but there appeared to be good action of the intercostal muscles and diaphragm. There was slight weakness of the right side of the face, but no other evidence of cranial nerve palsy, particularly nothing to suggest bulbar weakness. There was extreme tenderness of the muscles of the trunk and extremities on palpation and in active and passive movements. This interfered greatly with an accurate determination of motor power, but it was clear that there was weakness of all four extremities. The loss of power was greatest in the right arm and the left leg, and in these members there was selective weakness of muscle groups. The deltoid muscles were almost completely paralyzed in both arms. The extensor muscles of the right arm, forearm and fingers were completely paralyzed, while there was still slight contraction of the corresponding flexor muscles. In the

From the Department of Medicine, the University of Chicago.

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legs the extensor muscles of both ankles and the left knee were almost paralyzed; moderate power remained in the other groups. The right triceps, left biceps and radial reflexes were absent; the left triceps, right biceps and radial reflexes were present, but weak. The patellar reflexes were not obtained; the achilles tendon reflexes were fairly active and equal on the two sides. The plantar reflexes were of flexor type. There were no objective sensory disturbances. Urinalysis gave normal results. Routine blood counts showed 4,800 red cells, 77 per cent hemoglobin and 17,200 white cells, with a normal differential count. The Wassermann and Kahn reaction of the blood were negative. The spinal fluid pressure was 85 mm., with normal manometric readings. There were: 288 lymphocytes per cubic millimeter; a negative reaction for globulin; 109 mg. of total protein; 121.2 mg. of chlorides; a negative Wassermann reaction, and a gold curve of 0002321000. Broth cultures of the spinal fluid showed no growth.

Diagnosis.—A diagnosis of acute anterior poliomyelitis with pontile involvement was made. Not only did this appear to be definite on clinical grounds but it was further suggested by the fact that there was an epidemic of poliomyelitis of considerable severity in Chicago at this time. During the months of August and September 1937, 248 patients with the disease were admitted to the Municipal Contagious Disease Hospital.

Course.—Twenty cubic centimeters of poliomyelitis convalescent serum was given intrathecally and 25 cc. intramuscularly on the day of admission; 30 cc. was given intrathecally on the following day. The same pattern of extensive but segmental weakness and paralysis of the extremities persisted for the duration of the disease. In the middle period of the illness there was some general improvement of muscular strength, but later a decline. Both deltoid groups, the right triceps and right forearm extensor groups and both quadriceps muscles were almost completely paretic throughout the course of the illness. Within six weeks marked atrophy of all four extremities had developed. By measurement it was greater in the right arm than in the left and about equal in the legs.

With time, certain unusual and puzzling features complicated this otherwise typical poliomyelitic picture. First, there were severe and prolonged tenderness and pain of the muscles of the neck, trunk and extremities. The patient complained bitterly and continuously of this and for four weeks was frequently sleepless because of it. While it had improved greatly after eight weeks, the deep hyperesthesia never completely left him. No objective sensory disturbances were detected at any time during the illness. On September 22 the spinal fluid pressure was 300 mm. of water; on September 30, 550 mm.; on October 5, 470 mm. On October 6 the optic disks were swollen from 1 to 2 D. The papilledema persisted and increased, so that on November 10 the disks were elevated to 4 D. and there were extensive peripapillary hemorrhages and exudates; there was no arteriovenous nicking. Vision failed rapidly at this time. Headache was not present, in spite of the high spinal fluid pressures. On November 1 complete paralysis of the left external rectus muscle was observed. By November 12 the plantar reflexes had become extensor in type, and there were adductor and flexor contractures of the legs and contractures of the right arm which were far more extensive than would be anticipated at this stage of the usual form of poliomyelitis.

It was thought that the increasing intracranial tension was most likely secondary to a plastic adhesive process in the leptomeninges, with resultant blockage of the flow and absorption of the spinal fluid. Accordingly, the patient was transferred to the service of Dr. Paul C. Bucy, and a combined ventriculographic and encephalographic examination was made on November 13, in an attempt to

demonstrate the mechanism of the intracranial hypertension and with the hope that the supposed adhesions of the arachnoid might be opened up. These roentgenograms showed moderate dilatation of the lateral ventricles without associated dilatation of the third and fourth ventricles. There was air in the basal cisterns, but none over the convexity of the brain. Dye injected into the ventricle was recovered promptly from the lumbar subarachnoid space. Three subsequent encephalograms were made on November 19, December 7 and December 14, in further attempts to break down the adhesive process. The appearance of the later encephalograms was similar in all ways to that of the original ones, with a tendency to increase in the size of the ventricles. In none of them was any air visualized over the surface of the brain. This was taken to support the clinical impression of adhesive arachnoiditis.

Repeated urinalysis gave normal results until November 10, when a 1 plus reaction for albumin was obtained, with a few casts. A trace of albumin was found on only two subsequent occasions. Following the ventriculogram on November 13, the blood pressure was 190 systolic and 140 diastolic. The blood pressure ranged between this level and 140 systolic and 110 diastolic for the rest of the patient's life. It is not known when the elevation of blood pressure began. Urea clearance was 27 by the square root formula on November 12 and 23 on November 20. There was never cardiac enlargement, and the electrocardiogram was interpreted as normal.

There were almost daily elevations of temperature from 37.4 to 38 c. (99.3 to 100.4 F.) during the whole course of the illness. The pulse rate ranged from 110 to 120. It was never slow. After the last therapeutic encephalogram, on December 14, the patient suffered a severe reaction and became comatose; hyperpyrexia developed. He died on December 25, with a temperature of 41.6 C. (106.8 F.). A tabulation of the spinal fluid findings during the course of the disease follows.

Date	Pressure (Mm. of Water)	Cells (Lympho-cytes)	Pandy Reaction	Total Protein (Mg. per 100 Cc.)	Dextrose (Mg. per 100 Cc.)
9/ 9/37	85	288	—	109	..
9/11/37	...	450	..	...	..
9/12/37	...	1,030	..	...	..
9/13/37	...	180	..	...	..
9/20/37	...	38	..	...	..
9/22/37	300	20	..	...	70
9/30/37	550	40	..	...	..
10/ 5/37	470	32	..	...	..
10/ 7/37	300	42	..	164	52
10/10/37	300	32	..	...	..
10/24/37	270	12	..	83	..
11/15/37	295	..	..	...	..
11/17/37	370	..	..	...	..
11/19/37	600 (Sitting position)	4	..	289	..
11/24/37	380	..	..	...	..
12/ 3/37	220	4	+	35	..
12/ 5/37	310	11	Trace	33.2	..
12/10/37	350	10	+	...	..
12/12/37	280	14	Trace	31.3	..
12/16/37	240	..	..	40.4	..

Report of Autopsy.—Postmortem examination was limited to the brain and spinal cord.

Gross Anatomic Changes: The formaldehyde-hardened brain weighed 1,510 Gm. There was nowhere any thickening of the leptomeninges or other evidence of a plastic inflammatory process in this location, either over the convexity or

in the region of the basal cisterns. Considerable edema of the cerebral hemispheres was indicated by the wide, flat appearance of the convolutions and the narrow sulci. The brain was otherwise normal externally. In serial frontal sections through the hemispheres a uniform enlargement of the ventricular system, particularly of the lateral ventricles, was apparent. The foramens of Monro and the sylvian aqueduct were widely patent, and there was nowhere any obstruction in the ventricular channel. At the level of the posterior end of the third ventricle there was softening in the region of the substantia nigra bilaterally, with actual cavitation on the left side. There were no other visible changes on the cut surfaces except for punctate hemorrhages in the right occipital pole, the result of the old ventriculographic wound. The spinal leptomeninges, like those of the brain, were thin and transparent. The external appearance of the spinal cord was normal in

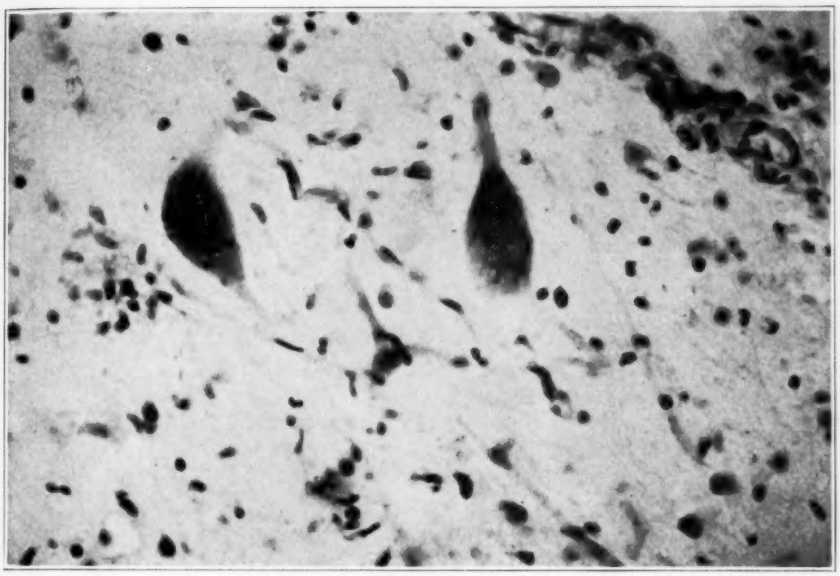

Fig. 1.—Anterior horn of the cervical portion of the cord, showing degenerating anterior horn cells, interstitial and perivascular infiltration of cells and glial reaction. Nissl stain.

every respect, but on cross section at all levels, cervical, dorsal, lumbar and sacral, there was gross damage of the gray matter, chiefly that of the anterior horns. In these regions the anterior gray matter was softened and had a glistening, spongy appearance. Although they extended from one end of the cord to the other, such changes were not continuous, but were much more marked on some cut surfaces than on others.

Microscopic Changes: Spinal cord: In Nissl and hematoxylin and eosin preparations for the eighth cervical segment the most striking change was the complete disappearance of nearly all ganglion cells of the anterior and posterior gray columns on both sides. Few, if any, of the cells which remained were normal; they appeared shrunken and angulated, stained deeply throughout and exhibted heavy clumping of the Nissl substance or complete tigrolysis (fig. 1). Associated

with this severe neuronal destruction was an intense reaction of the glia, consisting of a marked increase of glia nuclei, of all varieties, throughout the gray matter, with occasional accentuation of loose arrangement. In these preparations there were rarefaction of the white matter, especially at the periphery, and some diffuse glial proliferation throughout the white matter, but much less than in the gray substance. Here and there small microglial nodules of 18 to 20 cells were seen. The inflammatory reaction was principally diffuse and interstitial, but some blood vessels with lymphocytic infiltration were seen both in the gray and in the white matter.

In the eighth dorsal segment the changes were essentially the same as at the cervical level. No ganglion cells whatever remained in the right anterior horn, and few in the left. The cellular reaction was also much more intense in

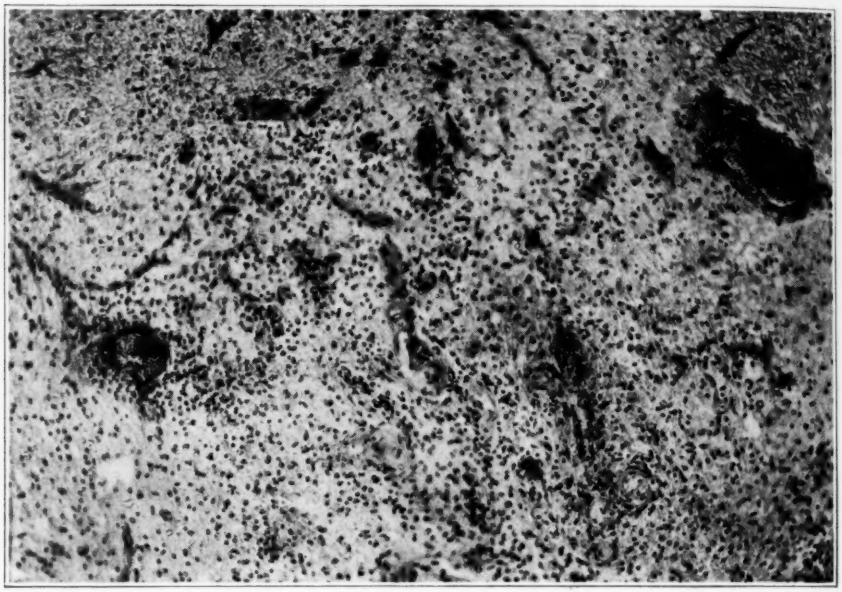

Fig. 2.—Anterior horn of the lumbar portion of the cord, showing complete absence of anterior horn cells, massive interstitial inflammatory reaction and thickened, infiltrated vessels. Hematoxylin and eosin stain.

the right anterior horn than in the left. Mixed with the glia nuclei of the inflammatory response were numbers of plasma cells, which infiltrated the gray matter diffusely and were not related to blood vessels. More ganglion cells remained in the posterior horns in this region than in the cervical, but all showed the type of degenerative change already described.

A similar picture appeared at the second lumbar level. A few degenerating cells remained in the posterior horns, and virtually none in the anterior, where the cellular reaction was intense on both sides, with striking interstitial infiltration of plasma cells, sometimes in groups (fig. 2). At the sacral level the changes were identical in kind but considerably less in degree. Numbers of anterior horn cells persisted on both sides, but most of them exhibited retrogressive changes of many kinds, including the swelling and vacuolation characteristic of the "severe

cell disease" of Nissl. It is noteworthy that there was nowhere any evidence of neuronophagia of the anterior horn cells, or even an increase of satellite glia cells. In a few places at all levels of the cord there were slight to moderate accumulations of lymphocytes around the meningeal vessels, but these were nowhere outstanding except at the sacral level, where they were much more heavy and diffuse.

The indications of involvement of the white matter with the Nissl and hematoxylin-eosin stains were substantiated by the myelin sheath preparations (fig. 3). Here, again, the greatest damage was in the gray matter. At all levels there was complete disruption of the myelin architecture in the anterior horns, where scarcely a single fiber was spared. At the lumbar level there was great paucity of

Fig. 3.—Lumbar portion of the cord. Note especially the total destruction of myelinated fibers in the anterior horns. Weigert-Pal stain.

fibers in the posterior horn and entrant zone of the posterior root as well, with the usual paleness, localized swellings and fragmentation of the surviving fibers. There was diffuse pale staining of the anterolateral columns of the white matter at all levels, increasing in degree from above downward. The posterior columns stained normally, or nearly so, at the lumbar and dorsal levels, but there was considerable degeneration of the columns of Goll in the cervical region. Correlated with this was partial degeneration of the lumbar posterior roots. There was no significant increase of glia fibers in Holzer preparations of the aforementioned levels of the spinal cord.

There were extensive alterations of the arteries of the meninges and the anterior and posterior roots, and of those within the gray matter of the cord at all levels. These consisted in great thickening of the walls and narrowing of the lumens. In some vessels this was due chiefly, if not entirely, to simple swelling of the intimal and medial layers. In others there was also proliferation

of the intima within the internal elastic membrane, a true endarteritis. In some instances the adventitia also was thickened, and occasional vessels of this sort showed infiltration of their walls with round cells. Vascular changes of this type were most frequent and severe in regions of greatest parenchymal damage to the cord, that is, in the anterior gray matter. Here a number of the arteries had become completely plugged by the intimal hyperplasia. In some the center of a concentrically thickened vessel was occupied by several large, swollen endothelial cells. In a few vessels hyaline thrombi partly or completely occluded the lumen. Most of the arteries with slight to moderate changes had an intact internal elastic lamina, but many of the more thickened ones showed extensive splitting of the elastica. Many exhibted an increase of the adventitial reticular fibers. This was true especially of the vessels showing perivascular and adventitial cellular

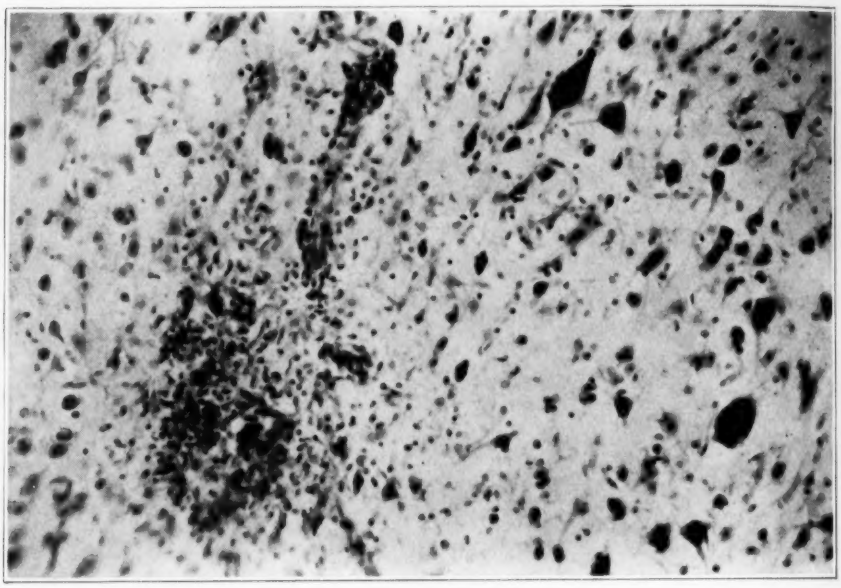

Fig. 4.—Area gigantopyramidalis from the right side, showing advanced degeneration of Betz cells and an inflammatory focus. Nissl stain.

infiltration. In regions of the anterior horns where there had been great parenchymatous destruction, new-formed capillaries were outlined with intercommunicating reticular networks.

Cerebral cortex: Representative sections were examined from the cortex and the white matter of the frontal, occipital and temporal lobes and the central convolutions of both sides. Changes were common to all these locations, but they were much greater in some places than in others. These consisted of widespread, and often marked, nonspecific retrogressive changes of the ganglion cells, chiefly swelling, chromatolysis and vacuolation of the cytoplasm. These were most extensive and diffuse in the right frontal and central regions and were most obvious in the Betz cells of the right precentral gyrus, where nearly all were so affected and showed also disruptive changes of the nuclei (fig. 4). It was in this locality also that the only cortical inflammatory reaction was seen. Around a number of

small veins were foci of destruction with a perivascular collar crowded with reacting glia cells—rod cells and other hyperplastic forms, and possibly some lymphocytes—resembling the perivenous foci of measles and vaccinia encephalitis. Such vessels were mostly deep within the cortex, along the layer of Betz cells, but occasionally one was encountered as superficial as the second cortical lamina. There were also universal alterations of the subcortical white matter. Everywhere in the hematoxylin-eosin preparations were mottled areas of paling and evidences of disintegration of myelin and edema. In some localities, notably the right postcentral convolution and the right frontal lobe, there was diffuse glial hyperplasia of the entire white matter with swelling of the cytoplasm of many of the glia cells, enormous gemästete astrocytes and huge vacuolated macrophages (fig. 5). Throughout there were also small nests of glia nuclei. There was one region of

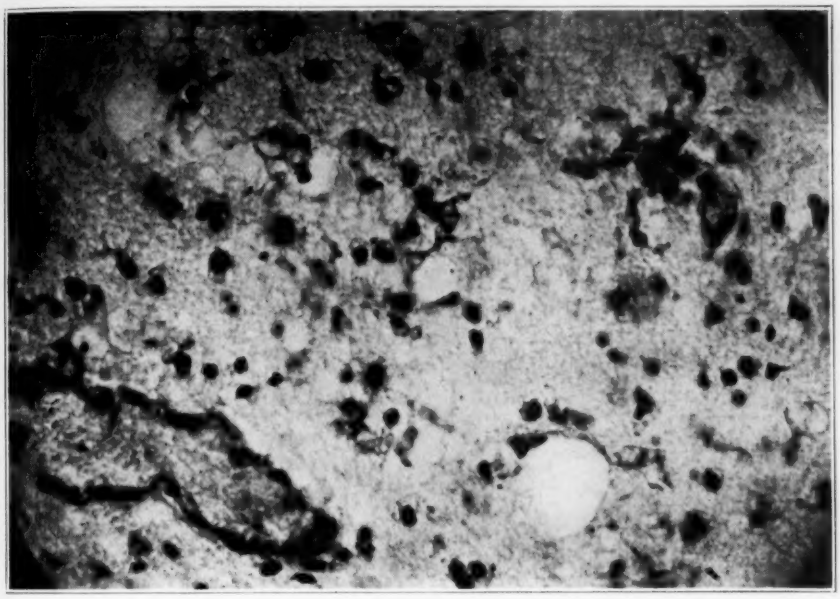

Fig. 5.—White matter of the right postcentral gyrus, with edema and progressive changes of the glia. Nissl stain.

actual softening with gitter cell formation in the right postcentral convolution. Wherever these changes in the white matter were at all striking, there were likewise slight infiltrations of lymphocytes around many of the smaller vessels. Thus, the type of glial reaction present was of the sort secondary to severe parenchymal damage of the white matter rather than that which occurs simply as a response to the presence of an infectious agent. Correspondingly, in myelin sheath preparations all the regions revealed more or less demyelination, which was often great (fig. 6). The areas of demyelination were not well circumscribed, but were patchy and merged in a worm-eaten way with regions of less severe change and with normal areas. In many places, especially in the more mottled areas, the demyelination appeared as a light halo around the vessels, but this was by no means the exclusive pattern of the demyelinating process. In fact, often the myelin imme-

diately around vessels appeared to be better preserved than that at a distance. Neither was there any tendency to sparing of the arcuate fibers, and in many regions the radiary and supraradiary networks in the cortex were damaged to the point of complete disappearance. In some places the myelin adjacent to the ventricle was completely degenerated, in other places well preserved. The degenerative changes of the individual fibers were advanced in many places, with the formation of myelin balls, but no focal softening was seen except for one small area, about 6 mm. in diameter, just beneath the cortex in the right central region. This small cavity was lined with gitter cells. With scarlet red stains of these demyelinated regions were seen scattered perivascular accumulations of fat in both the gray and the white matter, but nowhere any areas of massive release of fat. Here and there in sections from the cortex thickened arteries and

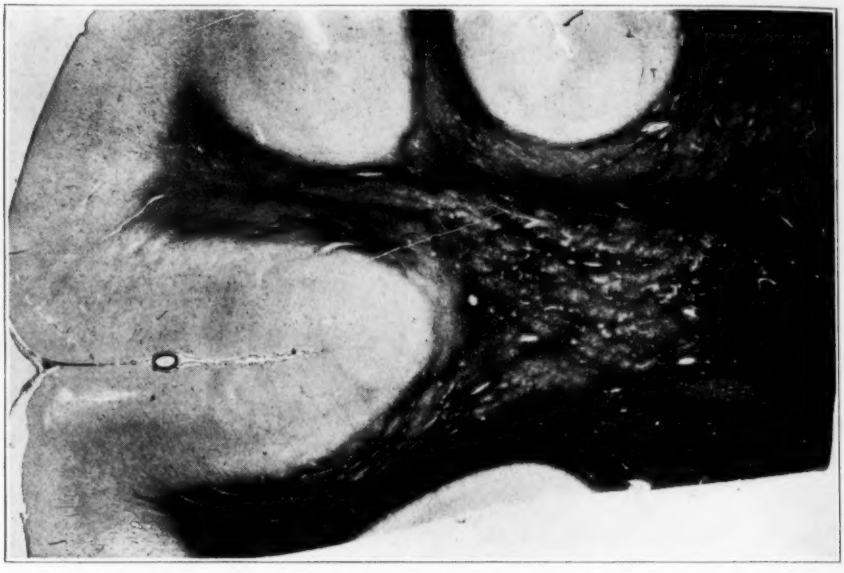

Fig. 6.—Right temporal region, showing diffuse demyelination. Weigert-Pal stain.

arterioles were seen both in the meninges and within the brain substance, but these were not numerous, and nowhere did they approach in degree those seen in the spinal cord or those to be described in the brain stem. There were no vascular changes, thromboses or endarteritic occlusions in the white matter to account for the demyelinating process.

Basal ganglia: In Nissl preparations there were retrogressive changes, diffusely distributed, of almost all the ganglion cells of the caudate nucleus, putamen and globus pallidus. These were severe, with fragmentation of the cytoplasm, displacement of nuclei or reduction to cell shadows. Clear shrinkage spaces were frequently seen around the small cells of the caudate nucleus. These parenchymatous changes were unaccompanied by any reaction on the part of the glia. There were light infiltrations of lymphocytes, plasma cells and macrophages around a few of the vessels of these nuclei, but they were not outstanding. There

was evidence of marked edema of the central white matter, and in some places, as in the ansa lenticularis, there was glial hyperplasia with bushy clumps of glia cells. In Spielmeyer stains for myelin there was no gross demyelination, focal or diffuse, and the individual myelin fibers were in good condition.

Brain stem: In Nissl preparations at numerous levels of the brain stem, diencephalon, midbrain, pons and medulla there were active degenerative changes of ganglion cells, generally in the form of swelling, chromatolysis and mild to severe nuclear changes. There was also neuronphagia of some of the more severely damaged cells. Alterations of this kind were distributed diffusely and were frequently observed in the body of Luys, the geniculate bodies, the red nucleus, the periaqueductal gray matter, the pontile nuclei, the reticular formation and the olives. The principal sensory and motor nuclei of the cranial nerves were relatively

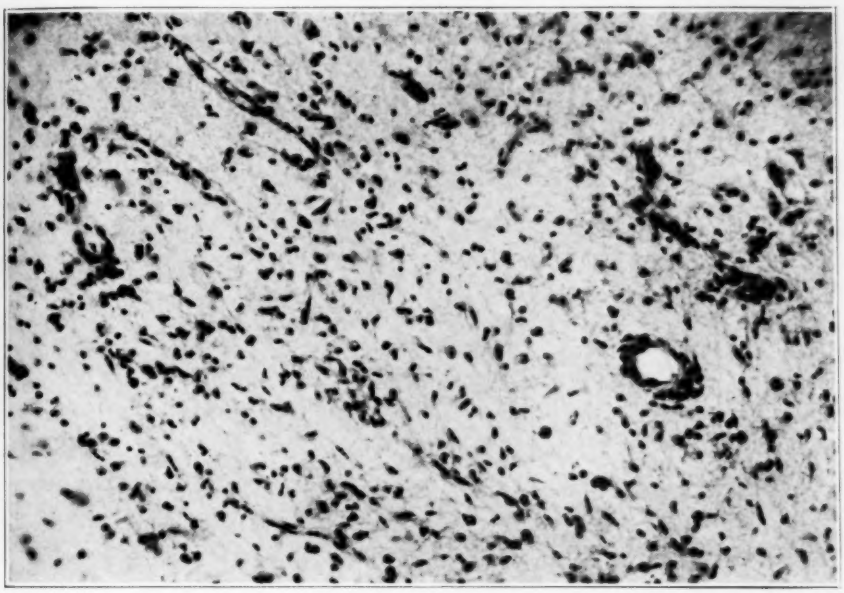

Fig. 7.—Tegmentum of the pons, showing diffuse inflammatory reaction of the glia and perivascular lymphocytic infiltration. Nissl stain.

intact. Here and there in the tegmentum of the pons, midbrain and medulla small focal regions of destruction were encountered, occupied by heavily proliferated glia, including rod cells, macrophages and sometimes gitter cells in considerable numbers. There was also everywhere more diffuse progressive reaction on the part of the neuroglia, with formation of Hortega cells, nodular accentuations of the hyperplastic nuclei and bushy clusters of oligoglia cells. Such were seen in both the gray and the white matter and in the basilar portion of the brain stem, as well as the tegmentum (fig. 7). Perivascular infiltrations of lymphocytes, and sometimes of plasma cells, were also a part of this diffuse inflammatory reaction. It was noteworthy in connection with the small foci of necrobiosis described that in several vessels with greatly thickened, infiltrated walls there was marked

hyperplasia of the intima to the point of occlusion. These were most often seen in or near the foci of destruction, but were also encountered in the meninges of the brain stem.

The most remarkable feature was the bilateral, symmetric, selective destruction of the substantia nigra (fig. 8). This was virtually complete and extended the entire length of the nucleus. The majority of the cells had disappeared, and the greater part of those which remained exhibited advanced retrogressive changes, including disruption and scattering of pigment. The region was the site of an inflammatory reaction unequaled in severity elsewhere in the brain. The vessels were heavily infiltrated with lymphocytes, plasma cells and macrophages. Within and around the lesions were signs of reparative activity in the form of hyper-

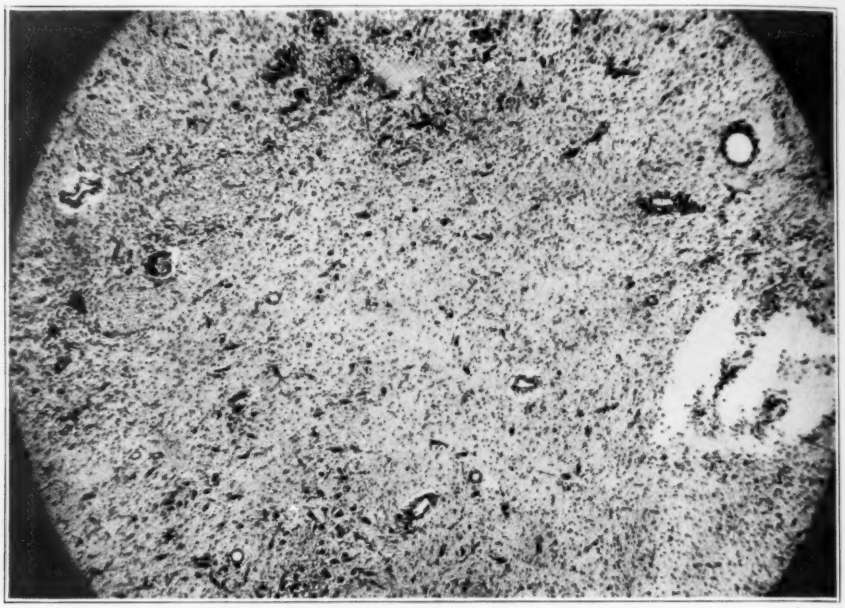

Fig. 8.—Substantia nigra, showing outfall of cells and small regions of cavitation. There is interstitial and perivascular inflammatory reaction. Nissl stain.

plastic astrocytes and proliferation of neuroglia fibers. It was evident that the focal necrosis depended on occlusion of the blood vessels of the region from proliferative arteritis and phlebitis. With the Van Gieson stain many of the vessels showed, in addition to the lymphocytic infiltration of the adventitia and media, enormous thickening of their walls, with complete blocking of their lumens from intimal proliferation of fibroblasts and endothelium (fig. 9). There was also considerable formation of new vessels. The white matter throughout the brain stem had an edematous appearance with the hematoxylin and eosin stain. In myelin sheath preparations from the pons and medulla, however, the myelin architecture appeared intact. At most there was diffuse paleness of the fiber staining.

Cerebellum: The changes in the cerebellum were relatively insignificant. There were mild, nonspecific, retrogressive changes of the cells of the dentate nucleus and of some of the Purkinje cells. There was also outfall of considerable

numbers of Purkinje cells in certain stretches, with well preserved strips between. The white matter of the medullary substance appeared edematous with the hematoxylin-eosin stain. There were generalized increase of glia nuclei in the white matter and bushy tufts of oligoglia cells. A few slight perivenous infiltrations of round cells were seen, limited to the white matter. Spielmeyer stains of the cerebellum for myelin revealed nothing abnormal.

Meninges: The leptomeninges of the cerebral hemispheres showed little infiltration, but there were in places slight accumulations of large mononuclear cells —apparently macrophages, since many of them contained granules of brown pigment. Around the brain stem there were patchy infiltrations of lymphocytes and large mononuclear cells resembling polyblasts. Alterations of the meningeal blood vessels have already been mentioned.

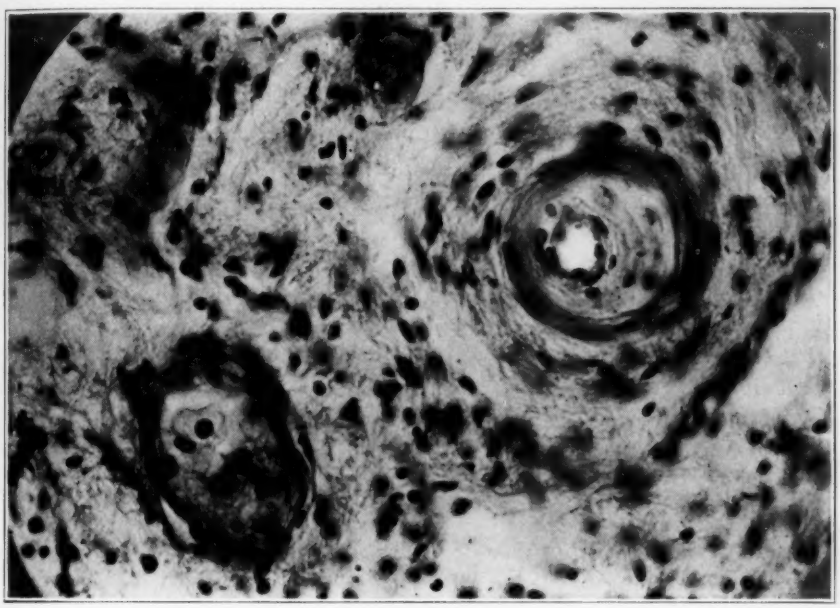

Fig. 9.—Blood vessels of the substantia nigra. Note the intimal thickening and plugs of swollen endothelial cells. Van Gieson stain.

COMMENT

The close similarity which exists between anterior poliomyelitis and other types of nonsuppurative infections of the nervous system, notably lethargic encephalitis, has been commented on frequently by writers who have described more or less atypical examples of the two conditions. Transitional forms exist, which are extremely difficult to identify or have been thought to be indistinguishable (Hauptli [1]). The present case

1. Hauptli, O.: Zur Histologie der Poliomyelitis und der Encephalitis epidemica (lethargica), Deutsche Ztschr. f. Nervenh. **71**:1, 1921.

is one in point. Nevertheless, in spite of the many anomalous circumstances, there are a number of reasons for regarding it as a case of true Heine-Medin disease. The acute febrile illness accompanied by selective amyotrophic paralysis of isolated muscle groups and diminution to absence of tendon reflexes, present in an uncomplicated form during the first weeks of the disease, was characteristic. This picture taken together with the typical spinal fluid findings and the occurrence of the symptoms during an epidemic makes the diagnosis of poliomyelitis inescapable. The discrepancies are in the later developments, notably the strikingly high intracranial pressure with papilledema. The late development of paralysis of the abducens nerve and of bilateral extensor plantar reflexes and the appearance of contractures at a much earlier date than would be expected in ordinary poliomyelitis are believed to be consequences of the cerebral edema and elevated intracranial tension. The idea that the increased intracranial pressure had been produced by an obstructive inflammatory process in the subarachnoid space was erroneous; it was to be attributed rather to the inflammatory edema present in the brain. The encephalographic findings were misleading in this regard. The vascular hypertension observed during the later period of the illness is difficult to interpret because of lack of pertinent clinical and pathologic information. It may be inferred from the urinary and cardiac findings that the hypertension was a late manifestation and played no significant part in the pathogenesis of the alterations in the nervous system. Whether it was produced by them or by vascular changes in the kidneys similar to those in the brain is unknown.

It is thought that the later course of the disease was altered by the encephalographic procedures and that the last of these was directly contributory to the fatal termination. This experience indicates again that air studies are to be avoided in cases of nonsuppurative inflammatory diseases of the brain, whether done for diagnostic or for theoretic therapeutic reasons.

Quite as many problems are raised by the pathologic as by the clinical aspects of the case. Primarily, polioencephalomyelitis extended from the spinal cord to the cerebral cortex and was expressed in terms of neuronal degeneration, inflammatory glial reaction and perivascular exudation. The inflammatory destruction, preferential for the anterior gray matter of the spinal cord, is consistent with an anatomic diagnosis of healing poliomyelitis. All those who have written on the comparative histopathologic features of poliomyelitis and of lethargic encephalitis have expressed agreement that the essential difference is seen in the massive destruction of the neurons of the anterior gray matter in poliomyelitis as contrasted with the incomplete and scattered damage to these elements

in lethargic encephalitis (Tobler,[2] Gerlach,[3] Harbitz,[4] Hassin[5]). In this respect the disease in the case at hand resembled true poliomyelitis. The scattered perivascular exudates, inflammatory glial reaction and damage to the ganglion cells present in the brain stem and cerebral cortex, notably the motor cortex, are likewise consistent with what has been described many times in cases of human and experimental poliomyelitis. The selective accentuation of the inflammatory destructive process in the substantia nigra is noteworthy. Harbitz and Scheel[6] recorded several instances in their extensive material of marked inflammatory changes in the pes pedunculi involving the substantia nigra and the red nucleus. They concluded that such localization, however, was exceptional. Goldstein[7] reported 2 similar cases, 1 that of a patient who died of the typical bulbar form of the disease. In neither case were there any symptoms during life to suggest involvement of the substantia nigra. Marinesco and his co-workers,[8] in their study of the Rumanian epidemic of 1927, noted perivascular and interstitial infiltrations and inflammatory glial reaction in and around the substantia nigra, with destruction and depigmentation of the substantia nigra itself similar to that seen in lethargic encephalitis. Alterations of this kind were observed in 16 of 28 cases and led these authors to speak of a mesencephalic form of poliomyelitis. One of the patients seen by them during this epidemic, an infant aged 1 year, presented flaccid paralysis of both legs, followed after seven weeks by tremors when at rest, akinesia, plastic rigidity and postural changes in the arms like those of parkinsonism. These symptoms subsided after three weeks, but the paralysis of the legs persisted.

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3. Gerlach, W.: Ueber Rückenmarksveränderungen bei Encephalitis lethargica, Berl. klin. Wchnschr. **57**:585, 1920.

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At no time did the patient in the present case manifest symptoms referable to the substantia nigra. It is possible that they were suppressed by the severe, diffuse injury of the peripheral neurons.

The obliterating, proliferative vascular changes with the focal regions of softening consequent to them which occupy so prominent a place in the histopathologic picture of this brain and cord are entirely foreign to anything hitherto described in the pathology of poliomyelitis. So, too, is the diffuse demyelination of the subcortical white matter. Taken alone, the latter feature might well be interpreted as the encephalitis periaxialis diffusa of Schilder. It is of the greatest interest to find leukodystrophy of this type associated with undoubted infectious polioencephalomyelitis, however one may classify the infection.

It appears that no final etiologic classification is possible on pathologic grounds. Whether one is dealing with true Heine-Medin disease, with encephalomyelitis of other and unknown virus origin or with a strange combination of the two remains uncertain. Such attempts as were made to identify an etiologic agent were unsuccessful. Repeated cultures of the spinal fluid gave no growth, and aerobic and anaerobic broth and blood agar cultures of the brain and spinal cord were likewise sterile. A monkey and mice inoculated intracerebrally with spinal fluid showed no symptoms. Inoculations of mice and monkeys with fresh brain tissue obtained at the ventricular puncture and with suspensions of brain and cervical portion of the cord obtained post mortem also gave negative results. The rhesus monkey inoculated with biopsy material from the brain died under ether anesthesia six weeks later. On histologic examination the brain and spinal cord of this animal were normal. The serum of the patient contained no neutralizing substances for the virus of the St. Louis type of encephalitis.

CONCLUSIONS

A case of poliomyelitis of unknown origin is described which is remarkable for the associated diffuse encephalitis and inflammatory changes in the blood vessels of the nervous system.

SODIUM DIPHENYL HYDANTOINATE IN TREATMENT OF CONVULSIVE SEIZURES

TOXIC SYMPTOMS AND THEIR PREVENTION

H. HOUSTON MERRITT, M.D.
BOSTON
AND
TRACY J. PUTNAM, M.D.
NEW YORK

Sodium diphenyl hydantoinate has been used at the neurologic clinic of the Boston City Hospital for the past two years. During this time we have administered the drug to more than 350 patients. A detailed report of the therapeutic results in 142 of these patients has been previously made,[1] and the statistics on the entire series up to date are now in the press. It is the purpose of this communication to give our opinion regarding the regulation of the dose and the treatment and prevention of toxic reactions.

In an attempt to evaluate the therapeutic efficiency of sodium diphenyl hydantoinate, it was thought advisable to use the drug only with patients who had received other forms of therapy, such as phenobarbital, bromides, a ketogenic diet, low fluid intake and surgical procedures and had not been relieved of their attacks. For the vast majority of our patients phenobarbital, sometimes in large but often in small and inadequate doses, had been the previous mode of therapy. A comparison of the therapeutic efficiency of sodium diphenyl hydantoinate with that of the previous modes of therapy in our patients is shown in the following tabulation.

	Percentage
Sodium diphenyl hydantoinate more effective	79
Previous therapy more effective	2
No form of therapy of value	13
Attacks too irregular for evaluation	6
	100

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From the Department of Neurology, Harvard Medical School, and the Neurological Unit, Boston City Hospital.

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1. Merritt, H. H., and Putnam, T. J.: Sodium Diphenyl Hydantoinate in the Treatment of Convulsive Disorders, J. A. M. A. **111**:1068-1073 (Sept. 17) 1938.

METHOD OF ADMINISTRATION

Sodium diphenyl hydantoinate is administered in capsules of 0.1 Gm. (1½ grains). The amount which should be given is that which will prevent the occurrence of the seizures and will not produce toxic symptoms. This amount must be determined by trial for each patient, and in our experience has varied between 0.2 and 0.6 Gm. (3 and 9 grains) daily. The rapidity of destruction of the drug is not known, but empirically it was found advisable to give it in divided doses. Because of the alkalinity of the drug, gastric symptoms—a heavy feeling in the epigastrium, nausea and anorexia—may result if it is given on an empty stomach. In such cases the medicine should be given with or just after meals. In occasional cases in which we have tried it, the administration of dilute hydrochloric acid, 15 minims (0.9 cc.), before meals has prevented the gastric symptoms without interfering with the effectiveness of the drug.

The sudden cessation of an established medication should be avoided. Since the mode of action of the various therapeutic agents used in the treatment of convulsive seizures is not necessarily similar, immediate withdrawal of an accustomed drug, phenobarbital for instance, may result in the occurrence of many seizures before a sufficient concentration of sodium diphenyl hydantoinate has been established. A satisfactory procedure is to continue the dose of the previous medicament for two or three days, then gradually to reduce it daily by fractions of 25 per cent of the original dose. The majority of adults can tolerate from 0.3 to 0.4 Gm. (4½ to 6 grains) of sodium diphenyl hydantoinate daily without any toxic symptoms. This should be given in doses of 0.1 Gm. (1½ grains) with each meal. If the attacks are relatively infrequent it may be advisable to start with 0.1 Gm. at the morning and evening meal, the third dose being added after a period of from seven to ten days. This dose, 0.3 Gm. (4½ grains), is often the optimum one, but should be increased if found inadequate. In such cases, 0.1 Gm., or if necessary 0.2 Gm. (3 grains), may be taken at bedtime with a glass of water or milk. We have encountered a number of patients who were not helped, or were only partly relieved of attacks, by a dose of 0.3 Gm. (4½ grains), but who were completely relieved by 0.4 or 0.5 Gm. (6 or 7½ grains). Rarely, patients have required 0.6 Gm. (9 grains) daily, usually given in doses of 0.2 Gm. (3 grains) with each meal. Such a dose is tolerated by only a small percentage of the patients, and larger doses are seldom, if ever, tolerated.

In special cases, when the attacks are known to occur at certain times, the drug can be administered so that the greatest concentration in the system is at that time. For instance, we have been able to prevent nocturnal attacks by giving most of the total dose before bedtime. Also, in the case of women who are prone to have attacks at the time

of their menstrual period we have made it a practice to give an additional 0.1 to 0.2 Gm. (1½ to 3 grains) on the critical days. This does not mean, however, that treatment can be limited to the night in patients with only nocturnal attacks or to the time of the menses in patients with attacks occurring only at this time. The attacks may be prevented at these times by the proper amount of therapy, but they may then be shifted to the daytime or to the intermenstrual period. It is necessary, therefore, that adequate treatment be given throughout the day and the entire month.

Regulation of the dose is not difficult in patients who are having several or many attacks weekly. Such patients are given 0.3 Gm. (4½ grains) daily. If this dose is found to be ineffective, it is increased by 0.1 Gm. (1½ grains) increments every ten days or two weeks until relief from attacks is obtained or until toxic symptoms develop. After the attacks have been controlled it is occasionally possible to reduce the dose without recurrence of attacks, but in the majority of such cases the reduction of even 0.1 Gm. (1½ grains) in the dose results in recurrence of attacks.

The treatment of patients who have relatively infrequent attacks is more difficult. Protection of these patients is important because of the danger of attacks interfering with their occupation or education. It is advisable that these patients receive more than the minimum amount of therapy, so that they may be protected under unusual circumstances. We have obtained good results in several such cases by giving 0.4 to 0.5 Gm. (6 to 7½ grains) of sodium phenyl hydantoinate daily, even though most attacks were prevented by a smaller dose.

TOXIC EFFECTS

Gastrointestinal System.—Gastrointestinal symptoms, such as a heavy feeling in the stomach or nausea and vomiting, are encountered in a small proportion of the patients. In the majority these symptoms are of a minor nature and can be prevented by giving the medicine with or at the end of the meal. In an occasional case these symptoms are very severe and it is impossible for the patient to retain the medicine or any food. Two such patients were able to take the medicine if 15 minims of dilute hydrochloric acid was given at the same time. Gastric symptoms were alleviated or prevented in many other patients by exposing the capsule to formaldehyde vapors for a few hours. Difficulty has been encountered in this method, however, with several patients, who were relieved of gastric symptoms but suffered a recurrence of attacks. In 1 such patient the capsules were found undissolved in the stools.

Central Nervous System.—Sodium diphenyl hydantoinate has little or no sedative action and cannot be used as a hypnotic, but evidences

of toxic action of the drug on the central nervous system can be obtained in practically all patients if the dose is sufficiently large. These symptoms are nervousness, tremor of the hands, ataxia, diplopia (with nystagmus) and occasionally drowsiness and headaches. Such symptoms usually develop in adults with a dose of from 0.5 to 0.6 Gm. (7½ to 9 grains) daily, and in children with smaller doses. The symptoms disappear as soon as the dose is reduced. Sometimes the dose may then be gradually increased without the recurrence of symptoms. Occasionally they can be prevented by distributing the dose more evenly over the twenty-four hours.

Psychoses developed in 2 patients after two and three months of treatment, respectively. Both patients were temporarily confined to state hospitals and were discharged as relieved, with a diagnosis of psychosis with epilepsy. The frequency of psychotic episodes in patients with convulsive seizures makes it difficult to evaluate the exact relationship of the psychosis to administration of the drug. Neither patient had experienced previous psychotic episodes, but the treatment was reinstituted in the case of the patient who had been helped by its previous use and has been continued now for one year, with complete relief of severe grand mal attacks and with no recurrence of the psychosis.

Cutaneous System.—Toxic dermatitis occurred in approximately 5 per cent of our patients. This reaction was most often seen in children or young adults, and varied from a mild erythema of the neck and arms to a more severe generalized morbilliform rash; a brawny, desquamating dermatitis developed in 1 adult, and a child, not under our care, had severe generalized dermatitis with the formation of blebs and subsequent desquamation. The more severe cutaneous reactions may be accompanied by fever and leukocytosis in the blood, with an increase in the eosinophils. The cutaneous reaction usually develops between the seventh and the fifteenth day of treatment, but may appear as early as the first day or as late as after several months. An increase in the growth of hair on the face, arms and torso has been noted by several female patients.

On the appearance of any cutaneous reaction the therapy should be immediately interrupted. Whenever it was thought that the drug had been effective in controlling the seizures, we reinstituted the therapy with patients showing the milder erythematous or morbilliform reactions without the redevelopment of the cutaneous reaction. It is inadvisable to continue the use of the drug in cases in which exfoliative dermatitis develops or in which a rash recurs with the reinstitution of therapy.

Gums.—Hypertrophy of the gums was noted in 6 per cent of our patients, and practically exclusively in children or young adults. It was not noted by the patient and was either found on examination or reported by the parents because they or their dentists had noted it. The

hypertrophy of the gums is different from that seen in patients with scurvy in that it is firm and not painful, there is no bleeding and the other symptoms of scurvy are not present. A slight decrease in the ascorbutic acid content of the serum has been reported [2] in children with this reaction who were attending a school for epileptic patients. The values were only slightly below normal levels; they were consistent with those found by other observers in patients confined to institutions and were probably due to a diet low in vitamin C.[3]

Hemopoietic System.—No severe disturbance of the hemopoietic system was noted in these patients. A slight degree of secondary anemia occurred in a small percentage of the patients, but considering the economic level of the patients, it is not possible to determine at present whether this anemia was due to treatment or to other factors.

There was no consistent change in the white blood count of the patients. In a few there was a transient reduction in the total number of white blood cells, but differential counts in such cases did not show any decrease in the polymorphonuclear leukocytes. Mild leukocytosis was present in a large number of the patients. Differential smears of the blood did not show anything remarkable, except for slight eosinophilia in a few of the patients. Six patients had more than 5 per cent of eosinophils. There was no evidence of diminution of the platelets.

Genitourinary System.—None of the patients complained of any symptoms in regard to urination, and studies of the urine gave normal results. Three patients experienced an increase in libido, and in 1 mentally deteriorated patient this symptom was so severe that we discontinued treatment.

General Effects.—The majority of the patients taking sodium diphenyl hydantoinate in doses of 0.3 Gm. or less daily tolerated the treatment with no symptoms. The majority of the reactions, exclusive of the cutaneous reactions, have been in patients in whom therapy was pushed beyond this point on account of the difficulty in controlling their attacks. The treatment was discontinued in 42 cases, for the following reasons: lack of cooperation by the patient or noneffectiveness of the drug, 36 cases; dermatitis, 3; psychoses, 1, and death, 2.

The causes of death of the 2 patients were miliary tuberculosis and suicide, respectively. The first patient was a boy aged 12 who had been suffering from attacks for three years and had been known to have pulmonary tuberculosis and tuberculous peritonitis for one year.

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2. Kimball, O. P.: Treatment of Epilepsy, J. A. M. A. **112**:1244-1245 (April 1) 1939.

3. Alexander, L.; Pijoan, M.; Schube, P. G., and Moore, M.: Cevitamic Acid Content of Blood Plasma in Alcoholic Psychoses, Arch. Neurol. & Psychiat. **40**:58-65 (July) 1938. Vitamin-C in State Hospital Patients and Personnel, Notes and Comments, Elgin State Hosp. Papers **3**:225, 1939.

He was relieved of convulsive attacks by sodium diphenyl hydantoinate, but died after an abdominal operation for tuberculous peritonitis. The other patient was a woman aged 30 who committed suicide by an overdose of phenobarbital after two months of therapy with sodium diphenyl hydantoinate. She had been depressed for several months before starting the treatment and had threatened suicide on several occasions.

SUMMARY

Sodium diphenyl hydantoinate is the most effective anticonvulsive drug that we have used. The toxic reactions which attend its use are of a different character from those observed with phenobarbital and the bromides. The drowsiness which the last two drugs produce and the rashes which often follow the use of bromides are rarely seen. Instead, a new group of symptoms is observed with high doses. Judging from animal experiments and clinical experiences so far, danger to life should be less than that from bromides or phenobarbital. The percentage of minor toxic reactions is probably greater than that encountered with other forms of therapy, such as phenobarbital. We believe the method should be tried with patients who are not free from symptoms with other forms of treatment.

PALLIDOFUGAL FIBERS IN THE MONKEY

S. W. RANSON, M.D.
AND
MARY RANSON, M.S.
CHICAGO

In a series of rhesus monkeys (Macaca mulatta) lesions were placed in the lateral part of the hypothalamus. Subsequent microscopic examination showed that the pallidofugal fibers of the ansa and fasciculus lenticularis had been interrupted and that the cells of the medial division of the globus pallidus had disappeared. Observations made on this material and on the brains of normal monkeys are briefly reported here.

MATERIAL AND METHODS

The operative procedures and the location of the lesions have been described elsewhere (Ranson [1]). The 11 animals used in this study were allowed to live for periods ranging from twenty-nine to seventy-eight days. The basal ganglia and mesencephalon were fixed in formaldehyde, embedded in pyroxylin, cut serially and alternate sections stained by the Weil method for fibers and with cresyl violet for cells. The extent and location of the lesions and the retrograde degeneration seen in the pallidofugal fibers have been described (Ranson [1]). The brains of 5 normal monkeys prepared in a similar manner were also available for study.

OBSERVATIONS

Pallidofugal Fibers.—In the normal rhesus monkey the ansa lenticularis (ventral part of the ansa lenticularis of von Monakow) is more sharply defined than in man. The fibers of the ansa emerge from the ventral surface of the medial division of the globus pallidus (figs. 1 and 2) and curve around its medial border, passing close to the fornix. Relatively few fibers from the internal medullary lamina enter the ansa, but it is joined by a few fibers which emerge from the medial border of the nucleus (fig. 1). The ansa then turns backward in the lateral part of the hypothalamus. Other fibers leave the medial division of the globus pallidus by passing through the internal capsule and become assembled in the fasciculus lenticularis, which joins the ansa (fig. 3). The large bundle formed from these two sources runs backward, passing close to the lateral side of the mamillothalamic tract

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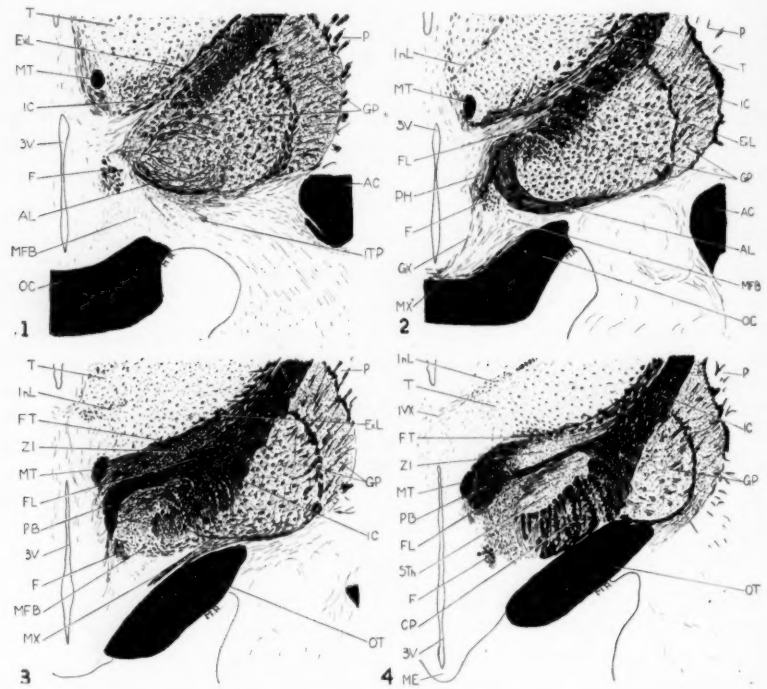
From the Institute of Neurology, the Northwestern University Medical School.

1. Ranson, S. W.: Somnolence Caused by Hypothalamic Lesions in the Monkey, Arch. Neurol. & Psychiat. **41**:1 (Jan.) 1939.

(fig. 4), and the constituent fibers become scattered through the field H of Forel (fig. 5). Their further course and termination could not be determined from the preparations at our disposal, but have been repeatedly and variously described by the authors cited in the accompanying footnotes. The fasciculus lenticularis is more like a plate than a bundle. Its anterior border is thick and rounded (fig. 3), but it becomes progressively thinner as it extends backward on the dorsal surface of the subthalamic nucleus of Luys (figs. 4 and 5).



Figs. 1-4.—Drawings from four frontal sections of the brain of a rhesus monkey, showing the course of the pallidofugal fibers. The following abbreviations appear in these figures and in figure 5: *AC* indicates the anterior commissure; *AL*, the ansa lenticularis; *CP*, the cerebral peduncle; *ExL*, the external medullary lamina; *F*, the fornix; *FL*, the fasciculus lenticularis (H_2); *FT*, the fasciculus thalamicus (H_1); *GP*, the globus pallidus; *GX*, the dorsal supraoptic decussation, or Ganser's commissure; *IC*, the internal capsule; *InL*, the internal medullary lamina; *ITP*, the inferior thalamic peduncle; *IVX*, the interventral commissure; *ME*, the median eminence; *MFB*, the median forebrain bundle; *MT*, the mamillothalamic tract; *MX*, the ventral supraoptic decussation, or Meynert's commissure; *OC*, the optic chiasm; *OT*, the optic tract; *P*, the putamen; *PB*, the pallidofugal bundle; *PH*, the pallidohypothalamic tract; *STh*, the subthalamic nucleus of Luys; *T*, the thalamus; *ZI*, the zona incerta, *3V*, the third ventricle.

The pallidofugal fibers are large. Since they stained deep blue, they formed conspicuous elements in the sections. None of them were seen in the lateral division of the globus pallidus. This part extended a considerable distance farther forward than the medial division, but in following through a series of sections none of these large, deep blue fibers were seen until the medial division was reached. It is certain that not many of these fibers run into the internal medullary lamina and through this into the ansa, but the possibility that some may do so is not excluded.

There has been a great deal of disagreement as to whether the ansa and fasciculus lenticularis are composed exclusively of pallidofugal fibers or whether they also contain fibers from the caudate nucleus and putamen (Bickel,[2] Foerster,[3] Jakob,[4] Foix and Nicolesco,[5] Kodama,[6]

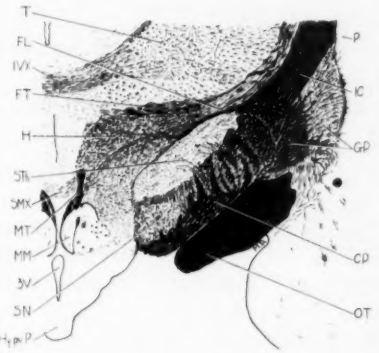


Fig. 5.—Drawing from a frontal section of the brain of a rhesus monkey showing the field H of Forel, into which the pallidofugal fibers run. Abbreviations are those used in figures 1 to 4. In addition, *H,* indicates the field *H* of Forel; *Hy. pv. P,* the nucleus hypothalamicus periventricularis posterior; *MM,* the medial mamillary nucleus; *SMX,* the supramamillary decussation, and *SN,* the substantia nigra.

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5. Foix, C., and Nicolesco, J.: Anatomie cérébrale: Les noyaux gris centraux et la région mésencéphalo-sous-optique, Paris, Masson & Cie, 1925.

6. Kodama, S.: Ueber die sogenannten Basalganglien, Schweiz. Arch. f. Neurol. u. Psychiat. **23**:38 and 179, 1929.

Lhermitte and Trelles,[7] Lotmar,[8] von Monakow,[9] Morgan,[10] Reise,[11] the Vogts [12] and Wilson [13]). Following Wilson, the majority of recent investigators have expressed the view that these bundles are derived from the globus pallidus. But Foix and Nicolesco and Lhermitte and Trelles traced some of the fibers from the caudate nucleus and putamen. Our observations, which will be presented in subsequent paragraphs, indicate that the fibers of the lenticular ansa and fasciculus arise exclusively from the globus pallidus, and in largest part, if not exclusively, from the medial division of the globus pallidus.

Pallidohypothalamic Tract.—This tract consists of fibers which run ventromedially into the hypothalamus at right angles to the fornix, passing either through this bundle or over its dorsomedial surface (fig. 2). The fibers spread out in the region of the ventromedial hypothalamic nucleus. These fibers lie somewhat caudal to those of the dorsal supraoptic decussation, or Ganser's commissure, and intermingle with them to some extent. The name pallidohypothalamic fasciculus was given by Bard and Rioch.[14] Krieg [15] described this bundle under the name "hypothalamic fasciculus" and stated that the fibers probably terminated in the ventromedial hypothalamic nucleus. Papez [16] also found them ending in this nucleus and stated that they come from the fasciculus lenticularis. That these fibers do come, in part at least, from the fasciculus lenticularis is shown by observations on our monkeys. The pallidohypothalamic tract was degenerated in all

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12. Vogt, C., and Vogt, O.: Zur Lehre der Erkrankungen der striären Systeme, J. f. Psychol. u. Neurol. (supp. 3) **25**:627, 1920.

13. Wilson, S. A. K: An Experimental Research into the Anatomy and Physiology of the Corpus Striatum, Brain **36**:427, 1914.

14. Bard, P., and Rioch, D. M.: A Study of Four Cats Deprived of Neocortex and Additional Portions of the Forebrain, Bull. Johns Hopkins Hosp. **60**:73, 1937.

15. Krieg, W. J. S.: The Hypothalamus of the Albino Rat, J. Comp. Neurol. **55**:19, 1932.

16. Papez, J. W.: Thalamic Connections in a Hemidecorticate Dog, J. Comp. Neurol. **69**:103, 1938.

those monkeys in which the lesions destroyed the fasciculus lenticularis. But in an animal (monkey 26) in which the pallidofugal fibers escaped injury except for some damage to the medial part of the pallidofugal bundle from the level shown in figure 4 caudally, the pallidohypothalamic tract was normal. Furthermore, in 2 (monkeys 19 and 48) in which the field H of Forel was destroyed at the level shown in figure 5 the pallidohypothalamic tract was normal, although the dorsal supraoptic decussation, or commissure of Ganser, was degenerated.

Finer Striofugal Fibers.—These fibers, obviously belonging to a different system, have been described for the brain of the rhesus monkey by Wilson [13] and Papez [17] and for the man by Reise.[11] These constitute Wilson's second group of striofugal fibers. He stated that fine fibers from the radial bundles of the globus pallidus edge obliquely across the basal third of the internal capsule and basis pedunculi to the subthalamic nucleus and substantia nigra. Papez traced these fibers from the caudate nucleus and putamen through the globus pallidus and basis pedunculi to the substantia nigra. In Weigert preparations he found that these fibers stained more lightly and with a somewhat different color than the pallidofugal fibers. These fine striofugal fibers could be readily identified in our preparations of the normal monkey's brain stained by Weil's method. They stained a light brownish blue, in sharp contrast to the deep blue of the fibers arising from the medial division of the globus pallidus. The majority of these fibers could be followed in large bundles obliquely through the basis pedunculi into the substantia nigra. Some of these bundles formed light transverse bands across the basis pedunculi, and from these bands fibers could be traced into the subthalamic nucleus through its ventrolateral surface (fig. 5). These finer striofugal fibers have been overlooked by most investigators of the corpus striatum. They were not damaged in any of our monkeys.

Cell Types.—The cells of the medial division of the globus pallidus were larger than those of the lateral division. In cresyl violet preparations they were fusiform, triangular or multipolar and had conspicuous dendrites. Satellite cells were present. The cells of the lateral division were more round or oval and had less conspicuous dendritic processes. They were surrounded by numerous satellite cells. Neuroglia cells were more numerous in the lateral than in the medial division. This accounts for the darker background of the lateral division in figure 7.

Monkey 20 may be selected as an example of animals with hypothalamic lesions so placed as to interrupt the ansa and fasciculus lenticularis. The location and extent of the lesions are illustrated in a previous article.[1] The animal had

17. Papez, J. W.: Reciprocal Connections of Striatum and Pallidum in the Brain of Pithecus (Macacus) Rhesus, J. Comp. Neurol. **69**:329, 1938.

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been allowed to live sixty-eight days, and retrograde or cellulipetal degeneration had occurred in the ansa and fasciculus lenticularis. The dorsal supraoptic decussation, or Ganser's commissure, was also degenerated. Any fibers which may enter the dorsal surface of the subthalamic nucleus from the fasciculus lenticularis could not have been damaged by the lesions.

The nerve cells of the medial division of the globus pallidus had almost completely disappeared. The remaining cells were pale and abnormal in appearance. The lateral division seemed normal. It was not possible, however, to be sure that a few cells of the lateral part may not also have been lost (fig. 6). The basal ganglion of Meynert remained intact. No evidence of cell loss could be seen in the caudate nucleus or putamen. A photomicrograph of a similar section

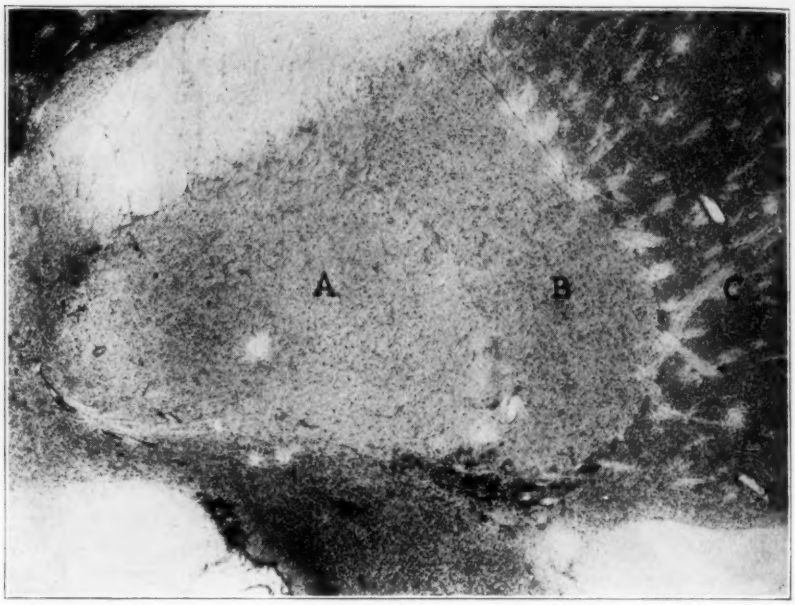

Fig. 6.—Photomicrograph from a frontal section of the brain of monkey 20. *A* indicates the medial division and *B* the lateral division of the globus pallidus, and *C*, the putamen. Cresyl violet stain.

from a normal monkey is shown for comparison (fig. 7). Monkeys 25, 39, 42 and 43 also had lesions interrupting the fasciculus lenticularis as well as the ansa, and the resulting cell loss was confined chiefly, if not entirely, to the medial division of the globus pallidus.

In another group (monkeys 6, 10 and 12) the lesions did not extend so far back and only the ansa lenticularis was destroyed, except for monkey 6, in which a few of the most anterior fibers of the fasciculus lenticularis were involved. In these 3 animals the cell loss was confined almost entirely to the anterior part of the medial division of the globus pallidus. These observations make it clear that the cells of origin of the fibers of the ansa are situated farther anterior than those from which the fasciculus lenticularis arises.

Evidence has been presented to show that the fibers of the ansa and fasciculus lenticularis arise from the cells of the medial division of the globus pallidus. It remains to be determined what becomes of the fibers arising from the cells of the lateral division. The Vogts [12] stated that isolated destruction of the lateral division caused such marked degeneration of the subthalamic nucleus as to suggest that the latter nucleus is at least preferably connected with this part of the globus pallidus. Support is given this idea by the fact that in our monkeys, in none of which the subthalamic nucleus or the striosubthalamic fibers were injured, the cells of the lateral division of the globus pallidus

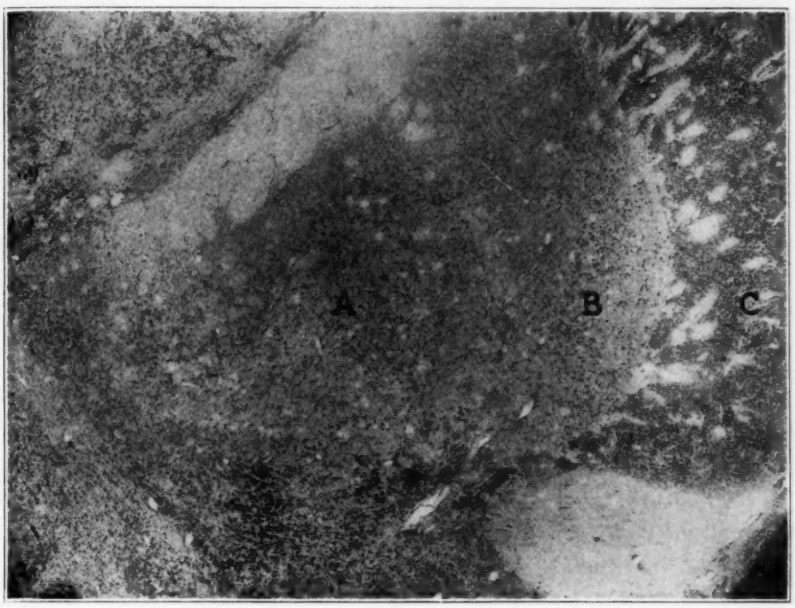

Fig. 7.—Photomicrograph from a frontal section of the brain of a normal rhesus monkey. *A* indicates the medial division and *B* the lateral division of the globus pallidus, and *C*, the putamen. Cresyl violet stain.

were normal. It must be remembered, however, that in the same monkeys the substantia nigra and the strionigral fibers were also uninjured.

Symptoms.—The drowsiness and emotional stolidity characteristic of monkeys with lesions of the ansa and fasciculus lenticularis have been attributed to the bilateral damage inflicted on the lateral hypothalamic area (Ranson [1]). The question must now be asked: Were there any symptoms that could be attributed to the bilateral interruption of the pallidofugal fibers of the ansa and fasciculus lenticularis?

There was no paresis or other gross disturbance of motor function, but the possibility exists that more detailed observations and testing might have revealed minor disturbances. The animals were able to run, jump and climb in an apparently normal manner, except that their movements were less spontaneous and much slower than those of a normal monkey. The lack of initiative was probably a part of the hypothalamic syndrome, but the slowness of movement may well have been pallidal in origin. The face was immobile and masklike, and this was probably, in part at least, attributable to the interruption of the pallidofugal fibers.

During the days following the operation, while the monkeys were somnolent, they showed a grasp reflex similar to that seen after removal of the premotor cortex. The monkeys, grasping a rod in their hands, could be lifted by the rod off the table and would hang in the air supported by their arms. If they were not too sleepy they would take part of the weight off the arms by swinging up the hind quarters, grasping the rod by the feet and hanging by all four extremities. It is noteworthy that this grasp reflex was as well developed in monkeys 6, 10 and 12, in which the fasciculus lenticularis was spared and only the ansa interrupted, as in those in which all the pallidofugal fibers had been interrupted.

Occasionally a hand resting on the animal could feel something resembling a myoclonic jerk, a sudden transient contraction of the skeletal musculature. Apparently these jerks involved the trunk musculature; the localization of the contractions was not accurately determined, however, and the limb muscles may have been involved.

There were no athetoid or choreiform movements, no tremor and no rigidity.

Comment.—It appears that the efferent fibers from the corpus striatum are separated into two distinct systems: (1) the large, heavily myelinated fibers of the ansa and fasciculus lenticularis, and (2) the finer, paler and more laterally placed fibers which descend to the substantia nigra and the subthalamic nucleus. Since it has been shown that monkeys in which the ansa and fasciculus lenticularis have been completely interrupted bilaterally do not show tremor, athetosis or rigidity, it is probable that these symptoms when present are due to involvement of the striatal system, the fibers of which terminate in the substantia nigra and, to a less extent, in the subthalamic nucleus. It is well known that in cases of chronic encephalitis with rigidity there is often more damage to the substantia nigra than to the pallidum. Since the fine, pale striofugal fibers pass through the pallidum on their way out of the striatum, it is obvious that they would be damaged with the pallidal system by lesions of the globus pallidus. In order

to get positive evidence of their function it will be necessary to interrupt them between the globus pallidus and the substantia nigra.

SUMMARY

Large deeply staining, myelinated fibers arising from the cells of the medial division of the globus pallidus form the ansa and fasciculus lenticularis. The pallidohypothalamic tract consists of fibers which run ventromedially into the hypothalamus, passing either through the fornix or over its dorsomedial surface.

Finer striofugal fibers, which probably arise in the caudate nucleus and putamen and possibly also in the lateral division of the globus pallidus, can be traced to the substantia nigra and the subthalamic nucleus.

The cells of the medial division of the globus pallidus are larger and more angular than those of the lateral division, and they disappear after interruption of the fibers of the ansa and fasciculus lenticularis.

Monkeys in which the ansa and fasciculus lenticularis have been interrupted bilaterally show no gross disturbance of movement. The movements, however, are slow and lacking in spontaneity. The faces of these monkeys are immobile and masklike.

DEMENTIA PARALYTICA

EFFECT OF CONTINUOUS INTENSIVE THERAPY WITH TRYPARSAMIDE AND BISMUTH ON CEREBROSPINAL SEROLOGIC REACTIONS AND FREQUENCY OF RELAPSE

GEORGE W. FORMAN, M.D.
ST. JOSEPH, MO.

Frequent relapses in cases of dementia paralytica having followed modern methods of treatment, it was decided to apply intensive and continuous treatment with tryparsamide and bismuth alone, or after malaria when feasible, until reversal of the serologic state of the cerebrospinal fluid occurred. Certain clinical evidences and opinions which lend justification to this procedure have presented themselves. I am aware of no other series in which treatment has been intensive and continuous until the Wassermann reactions of the spinal fluid became negative or until death supervened.

MATERIAL

Thirty-eight patients with dementia paralytica were treated from April 4, 1930 to Sept. 13, 1938; all were women. The following were common factors in treatment: First, tryparsamide was administered in doses of 3 Gm. continuously each week, except for two weeks twice each year preceding examinations of the blood and spinal fluid; second, thio-bismol, in doses of 0.02 Gm., was given twice a week for six week periods, alternating with rest periods of six weeks; third, this treatment was continued until the Wassermann reaction of the spinal fluid was negative, and in many cases until the serologic condition of the blood was also negative, although the former is the important factor. In addition, and undoubtedly a major factor in determining the outcome, malarial therapy was administered to 32, or 84.2 per cent, of the patients. The group was representative of the average type of cases of dementia paralytica, usually advanced, in which commitment is necessary. The duration of mental symptoms varied from three weeks to three years. Many patients had received inadequate treatment at varying intervals and for varying periods preceding admission. The Wassermann reaction of the spinal fluid was 4 plus in all but 2 cases, in each of which it was 2 plus. Colloidal gold tests of the spinal fluid showed curves typical of dementia paralytica in all but 4 cases, in which modified curves for dementia paralytica and syphilis were present; reactions for globulin were positive in all; the cell counts ranged from 5 to 179.

RESULTS

In the accompanying chart are shown the dates of admission, the relative periods necessary for continuous intensive treatment to bring about negative Wassermann reactions of the spinal fluid, the relative periods during which the

Wassermann reactions have remained negative and, for 1 patient (case 13), the period elapsing before the Wassermann reaction of the spinal fluid reverted to positive. The time that has elapsed since the beginning of treatment varies from approximately eight and one-half years to slightly over one and one-half years. The period required for continuous intensive treatment to obtain serologic reversal of the spinal fluid varied from ten months to seven years; cases 33 and 1, respectively, representing these two extremes, are classed as instances of clinical remis-

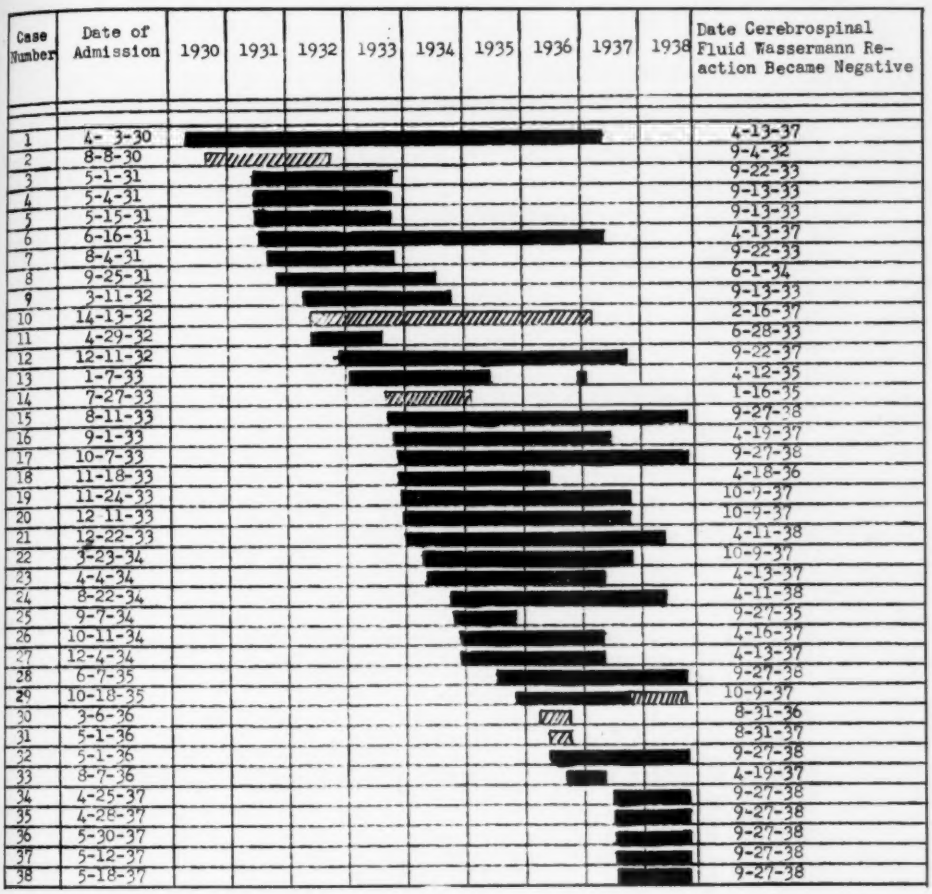

Chart showing clinical data on 38 patients with dementia paralytica treated continuously and intensively with tryparsamide and bismuth. In this chart, black rectangles indicate the time from admission until the Wassermann reaction of the spinal fluid became negative; the diagonally ruled sections, the time from admission until death supervened. In the latter cases the Wassermann reaction of the spinal fluid was still positive.

In case 12 the vertical bar denotes the time when the Wassermann reaction of the spinal fluid reverted to positive; in case 29, the diagonally ruled section denotes time elapsing after the Wassermann reaction of the spinal fluid became negative before the patient died of pulmonary tuberculosis.

sion; in each the Wassermann reaction of the spinal fluid has remained negative for one and one-half years, and in each the formula typical of dementia paralytica prevailed at the beginning of treatment. The clinical remission in case 1 has been maintained for eight and one-half years, since soon after treatment with malaria at the beginning of illness. Eleven patients, or 28.9 per cent, have returned to their former social and domestic levels; 7 patients, or 18.4 per cent, show partial remissions and are outside the hospital; 14 patients, or 36.8 per cent, are in the hospital and are unimproved or slightly improved, although the disease is arrested; 6 patients, or 15.8 per cent, are dead. There have been no clinical relapses, and the only evidences of progression of the disease have been in patients who died. It is assumed that the absence of, or only slight, improvement is due to destruction of functioning tissues.

Of the 6 patients who are dead, 2 are known to have died of causes other than dementia paralytica. One died of carcinoma of the uterus while treatment for dementia paralytica was in progress and the Wassermann reaction of the spinal fluid was still positive; the other died of pulmonary tuberculosis one year after the Wassermann reaction of the spinal fluid had become negative, and at a time when the serologic reaction of the spinal fluid was still negative. This leaves 4 patients, or 10.5 per cent, who died of dementia paralytica.

In 1 patient (case 13), 2.6 per cent of the entire series or 3.1 per cent of all those who are living and whose Wassermann reactions of the spinal fluid had become negative, the reaction reverted to positive after one and one-half years. This patient had received malarial treatment in the beginning, and a clinical remission had been recorded; she was still in a state of clinical remission at the time when the Wassermann reaction again became positive. She drifted into other hands, and I have been unable to follow her progress since. This case, however, indicates the necessity of examinations of the spinal fluid at regular intervals for years after negative Wassermann reactions have been obtained.

At the time when the Wassermann reaction of the spinal fluid became negative the colloidal gold formula had been reduced entirely to zero in 16 cases, or 42.0 per cent, and in only 3 cases was there a figure above 2. As time passes these persistently abnormal curves tend to return to normal. The highest cell count recorded at the time when the Wassermann reaction became negative was 12, and in the majority the cell count was under 6.

COMMENT

Modern effective methods of treatment of dementia paralytica had origin with the introduction of malarial therapy by Wagner von Jauregg in 1917. In 1923 tryparsamide was first reported on clinically by Lorenz, Loevenhart, Bleckwenn and Hodges,[1] but much time elapsed before its true value was recognized because of the fear of ocular complications. King and Cocke,[2] in 1930, published a report describing the technic of producing artificial fever by high frequency currents, after having treated

1. Lorenz, W. F.; Loevenhart, A. S.; Bleckwenn, W. J., and Hodges, F. J.: Therapeutic Use of Tryparsamid in Neurosyphilis, J. A. M. A. **80**:1497 (May 26) 1923.

2. King, J. C., and Cocke, E. W.: Therapeutic Fever Produced by Diathermy, with Special Reference to Its Application in the Treatment of Paresis, South. M. J. **23**:222 (March) 1930.

20 patients with dementia paralytica. Other methods of treatment, employing infectious and artificially produced fevers, have from time to time been introduced. Rat bite fever (soduku) was first employed by Solomon and his associates [3] in 1926, recurrent fever by Plaut and Steiner [4] in 1920, typhoid vaccine (foreign protein) by Kunde, Hall and Gerty,[5] the electric blanket by Wilgus and Lurie,[6] hot baths by Mehrtens and Pouppirt [7] and subjection of the patient to heated circulating conditioned air by Simpson and his collaborators [8] and others.

Years have now passed, and the literature concerned with evaluation of these forms of treatment and their combinations has become voluminous. From this literature, malarial therapy, artificially induced fever, either by diathermy or by hyperthermia, and chemotherapy with tryparsamide and the heavy metals hold the spotlight with regard to desirable results, each method having its adherents.

Of practical interest has been considered the permanency of results. Most reports have to do with the results soon after treatment. Many other reports, made after a period of years, have failed to make clear the percentages of relapse. It is evident, however, that clinical remissions after these forms of treatment, are followed by relapse in a significant proportion of cases.

Hinsie and Blalock [9] showed that from four to seven years after treatment with malarial therapy alone 43.8 per cent of a series of 105 patients had died and only 21 per cent were in a state of clinical remission, as compared with the usual 30 to 35 per cent in a state of remission within from a few months to one year after treatment. Yule [10] in a report on 100 consecutive patients with dementia paralytica

3. Solomon, H. C.; Berk, A.; Theiler, M., and Clay, C. L.: The Use of Soduku in the Treatment of General Paralysis, Arch. Int. Med. **38**:391 (Sept.) 1926.

4. Plaut, F., and Steiner, G.: Recurrensinfectionen bei Paralytikern, Ztschr. f. Neurol. u. Psychiat. **53**:103, 1920.

5. Kunde, M. M.; Hall, G. W., and Gerty, F. J.: Nonspecific Protein Therapy in General Paralysis: Preliminary Report, J. A. M. A. **87**:1376 (Oct. 23) 1926.

6. Wilgus, S. D., and Lurie, L.: The Fever Treatment of Paresis by Means of the Diathermy Current and the Electric Blanket, Illinois M. J. **60**:341 (Oct.) 1931.

7. Mehrtens, H. G., and Pouppirt, P. S.: Hyperpyrexia Produced by Baths: Its Effect on Certain Diseases of the Nervous System, Arch. Neurol. & Psychiat. **22**:700 (Oct.) 1929.

8. Simpson, W. M.: Artificial Fever Therapy of Syphilis, J. A. M. A. **105**:2132 (Dec. 28) 1935.

9. Hinsie, L. E., and Blalock, J. R.: Treatment of General Paralysis: Results in One Hundred and Ninety-Seven Cases Treated from 1923-1926, Am. J. Psychiat. **11**:541 (Nov.) 1931.

10. Yule, L. W.: Changes in the Course of Dementia Paralytica Under Malarial Therapy, Ohio State M. J. **27**:139 (Jan.) 1931.

who were treated with malaria followed by arsenicals and mercury for from three to six months only, showed that soon after treatment 46 per cent had good remissions and 24 per cent partial remissions, all 70 per cent having returned to their homes. After slightly more to slightly less than five years after treatment, a check revealed that 43 per cent had died, 41 per cent were in a hospital and only 16 per cent were still outside a hospital. Stanley [11] reported on a series of 181 patients with dementia paralytica who had been treated with malaria alone; presumably, soon after treatment 28.7 per cent had been discharged with complete remissions and 18.3 per cent with partial remissions; 21.5 per cent remained in hospital and 41.3 per cent had died. A check four to six years later of the status of the 37 per cent of patients who had been discharged revealed only 9.4 per cent still with complete remissions and 10.5 per cent with partial remissions. Reid [12] reported a rate of remission of 31 per cent following treatment with malaria alone in a series of 225 cases over a period of nine years. A check showed that the patients treated six to nine years previously showed a reduction of this rate to 12 per cent and the patients treated one to five years previously a decrease in the percentage of recoveries to 24 per cent. Also there was an advance in the number of deaths from 24 per cent one year after treatment to 78 per cent nine years after. In a follow-up study of 126 patients with dementia paralytica from one to ten years after malarial treatment, many of the patients having been treated subsequently with potassium iodide and bismuth while others received little or no treatment, Wile and Hand [13] showed that 50.1 per cent were still in a state of remission to the extent that most were working at previous or modified occupations. However, 22.3 per cent had died "presumably as a result of the progression of the diseases"; 28.6 per cent were unimproved or progressively deteriorating, and 16 per cent had become institutionalized. This report does not state specifically, but indicates, that these patients had relatively early stages of the disease. At some variance with the foregoing reports is that of Freeman, Eldridge and Hall,[14] which indicates

11. Stanley, A. M.: The Present Status of One Hundred and Eighty-One Cases of General Paralysis Four or More Years After Treatment with Malaria, Psychiatric Quart. **6**:310 (April) 1932.

12. Reid, B.: General Paralysis: Results of Eight Years of Malarial Treatment, J. Ment. Sc. **78**:867 (Oct.) 1932.

13. Wile, U. J., and Hand, E. A.: Ten Years' Experience with Malaria in Neurosyphilis: A Critical Appraisal, Am. J. Syph., Gonor. & Ven. Dis. **20**:63 (Nov.) 1936.

14. Freeman, W.; Eldridge, W. W., and Hall, R. W.: Malaria Treatment of Dementia Paralytica: Results in Two Hundred and Five Cases After Five to Eleven Years, South. M. J. **27**:122 (Feb.) 1934.

that of 195 patients with dementia paralytica treated five to eleven years previously 31 per cent were still outside a hospital, 39 per cent were still hospitalized and 30 per cent were known to be dead. The fact that the frequency of relapse in the patients discharged was practically negligible was stressed by these authors and was ascribed to early treatment and more paroxysms of fever. Even so, it seems possible that the 30 per cent of deaths may represent in part progression of the disease.

The literature indicates that patients for whom malarial treatment has been supplemented by continuous or routine administration of tryparsamide in conjunction with the heavy metals have fared much better as regards freedom from relapse and arrest of the disease. Solomon and Epstein [15] reported a series of 173 cases in which the common factor of therapy was malaria, supplemented with various forms of treatment, chiefly administration of tryparsamide and often the heavy metals (bismuth and mercury). From three to nine years after the beginning of treatment remissions were present in 36.4 per cent of patients and partial remissions in 12.1 per cent; 15 per cent were improved but hospitalized; 13. 8 per cent were unimproved, and 16.7 per cent were dead. The series of 32 patients of Hinsie and Blalock [9] treated with combined malaria, tryparsamide and mercury, even though patients who did not do well with malaria alone and for whom tryparsamide therapy was not instituted until six months or longer after malaria treatment was concluded, showed a death rate of 28.7 per cent, or 16.3 per cent less than those treated with tryparsamide alone and 15.1 per cent less than those treated with malaria alone. O'Leary and Welsh [16] obtained excellent results in 186 cases of advanced dementia paralytica in which malarial treatment was used and followed either by tryparsamide and bismuth or a course of intraspinal treatment combined with arsphenamine and bismuth or mercury. Clinical relapse occurred in only 2.6 per cent. The length of time during which this supplementary treatment was continued was not stated.

While it is generally agreed that improvement in the spinal fluid does not parallel the clinical improvement following the accepted methods of treatment, reversal of the serologic reactions to normal soon after treatment seems especially desirable as a greater security

15. Solomon, H. C., and Epstein, S. H.: Dementia Paralytica: Results of Treatment with Malaria in Association with Other Forms of Therapy, Arch. Neurol. & Psychiat. **33**:1008 (May) 1935.

16. O'Leary, P. A., and Welsh, A. L.: Treatment of Neurosyphilis with Malaria: Observations of Nine Hundred and Eighty-Four Cases in the Last Nine Years, J. A. M. A. **101**:498 (Aug. 12) 1933.

against relapse or progression. Solomon and Epstein,[17] referring to the tryparsamide treatment of neurosyphilis, said:

> The ideal is to have both clinical improvement and serological cure. . . . We are very strongly of the opinion that the cases which show clinical improvement without concomitant serological improvement are quite likely to relapse. . . . It is our opinion that the cases which show complete serological cure are likely to have a complete arrest of the activity and if clinical improvement has not occurred, it is because damage to functioning elements prevents improvement.

Freeman, Eldridge and Hall[14] stated: "A persistently positive spinal fluid is a good indication that the process has not been terminated and the deterioration will progress."

Of a series of 26 patients with dementia paralytica, reported on by Goodman and Moore,[18] who showed persistently positive reactions of the cerebrospinal fluid, relapse occurred in 10, or 38.4 per cent. In another group of 11 patients, in which a reversal of reaction occurred, there were no relapses. These patients all received continuous treatment for from six months to more than two years. Of the 20 patients who received fever therapy, only 1 had a relapse, and this patient showed a persistently positive reaction of the spinal fluid. Their report also shows convincingly the reduction in the percentage of relapses when treatment is continued longer than two years, as compared with that when treatment is continued for from six months to more than two years.

SUMMARY

Thirty-eight patients with dementia paralytica were treated intensely and continuously, for periods varying from ten months to seven years, with the maximum doses of tryparsamide and thio-bismol until the Wassermann reactions of the spinal fluid were negative or until death supervened. Eighty-four per cent of this group also received malarial treatment in the beginning. Of the series, 28.4 per cent showed complete and 18.4 per cent partial remission; 36.7 per cent were unimproved or slightly improved; 5.2 per cent died of causes other than dementia paralytica, and 10.5 per cent died presumably of dementia paralytica.

Two and six-tenths per cent of the entire group after showing a negative Wassermann reaction of the spinal fluid had a reversal to positive.

In all of the 84.2 per cent who are living, reversal of the Wassermann reaction of the spinal fluid to negative was effected.

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17. Solomon, H. C., and Epstein, S. H.: Tryparsamide in Treatment of Neurosyphilis, New York State J. Med. **31**:1012 (Aug. 15) 1931.

18. Goodman, M. J., and Moore, J. E.: Persistent Abnormalities (Wassermann-Fastness) of the Spinal Fluid in Treated Neurosyphilis: Their Prognostic Import, Arch. Int. Med. **55**:826 (May) 1935.

There have been no clinical relapses. The only evidences of progression are represented by deaths due to dementia paralytica in 10.5 per cent of the patients.

CONCLUSIONS

Results with this series bear out the opinion and clinical evidence that although clinical improvement in dementia paralytica following modern methods of treatment shows no relation to the degree of improvement in the spinal fluid, nevertheless a reversal of the Wassermann reaction of the spinal fluid to normal is an especially desirable feature with regard to the probability of relapse or progression.

The observations also indicate, first, that continuous and intensive treatment with tryparsamide and the heavy metals, until the Wassermann reaction of the spinal fluid is negative, whether or not fever treatment has been given, is effective in preventing relapse or progression while treatment is in progress; second, that it is effective in promoting the serologic reversal in the spinal fluid to normal in 100 per cent of those who do not die of the disease before the Wassermann reactions of the spinal fluid become negative, and, third, that it reduces the incidence of progression of the disease, as evidenced by death—in this series to only 10.5 per cent. Also in this series the chances of negative Wassermann reactions of the spinal fluid becoming positive again are 3.1 per cent, an indication of the necessity of examinations of the spinal fluid at regular intervals for years following the obtaining of a negative reaction.

A longer period of observation in these cases is desirable.

CELLS OF ORIGIN OF FIBERS OF CORPUS CALLOSUM

EXPERIMENTAL AND PATHOLOGIC OBSERVATIONS

L. J. PINES, M.D.
AND
R. M. MAIMAN, M.D.
LENINGRAD, U.S.S.R.

There is available no exact information in regard to the origin of the commissural fibers of the corpus callosum (Cajal,[1] von Kölliker,[2] Dotto and Pusateri,[3] Lévi-Valensi,[4] de Vries,[5] Van Valkenburg,[6] de Villaverde [7] and Lorente de Nó [8]). In this investigation we have used the method of retrograde cell degeneration, which until now has rarely been employed for the study of this problem. The material consisted of the brains of dogs in which the corpus callosum had been divided or areas of the cerebral cortex extirpated, and of human brains with focal lesions of the cortex.

EXPERIMENTAL OBSERVATIONS

Methods.—Operations were performed with sterile precautions on dogs under morphine anesthesia. At a distance of 0.5 cm. from the midline an opening, 1 cm. in diameter, was made with a trephine. This was enlarged with forceps parallel to the midline. The breadth of the opening was nearly 2 cm. After the dura mater

1. Ramón y Cajal, S.: Sur la structure de l'écorce cérébrale de quelques mammifères, Cellule **7**:34, 1891; Histologie du système nerveux de l'homme et des vertébrés, translated by L. Azoulay, Paris, A. Maloine, 1909.

2. von Kölliker, A.: Handbuch der Gewebelehre des Menschen, ed. 6, Leipzig, Wilhelm Engelmann, 1896, vol. 2, p. 664.

3. Dotto and Pusateri: Sul decorso delle fibres del corpo calloso e del psalterium, Riv. di pat. nerv. **2**:64, 1897.

4. Lévi-Valensi: Le corps calleux, Thesis, Paris, 1910.

5. de Vries, J.: Ueber die Cyto-Architektonik der Grosshirnrinde der Maus und über die Beziehungen der einzelnen Zellschichten zum Corpus callosum auf Grund von experimentellen Läsion, Folia neurobiol. **6**:289, 1912.

6. Van Valkenburg, C. T.: Experimental and Pathologico-Anatomical Researches on the Corpus Callosum, Brain **36**:119, 1913.

7. de Villaverde, J. M.: Estudios anatómico-experimentales sobre el curso y terminación de las fibras callosas, Trab. d. lab. de invest. biol. Univ. de Madrid **19**:37, 1921; Sobre el origen de las fibras callosas en el Area Gigantopyramidalis del conejo, ibid. **19**:195, 1921; Ueber die Endigungsweise der Balkenfasern in der motorischen Rinde bei der Fledermaus, Zentralbl. f. d. ges. Neurol. u. Psychiat. **65**:162, 1932.

8. Lorente de Nó, R.: La corteza cerebral del ratón, Trab. d. lab. de invest. biol. Univ. de Madrid **20**:41, 1923.

was cut, one hemisphere was drawn laterally with a flexible spatula. The spatula was then carefully lowered along the medial surface of the hemisphere, and the corpus callosum was cut in the sagittal direction. Bleeding was controlled by carefully filling the space between the two hemispheres with tampons, which were later removed. The defect in the bone was covered with fascia and soft tissues. The opening in the skin was closed and a dressing applied. Usually the animals bore the operation badly, but after from twenty-four to forty-eight hours they were able to stand and could be coaxed to eat. Young animals stood the operation better than the older ones. After from fourteen to twenty days the animals were killed with chloroform and the brains removed and placed in fixing fluid. Sections, 10 or 12 microns in thickness, were cut in paraffin or in pyroxylin and stained by Nissl's method.

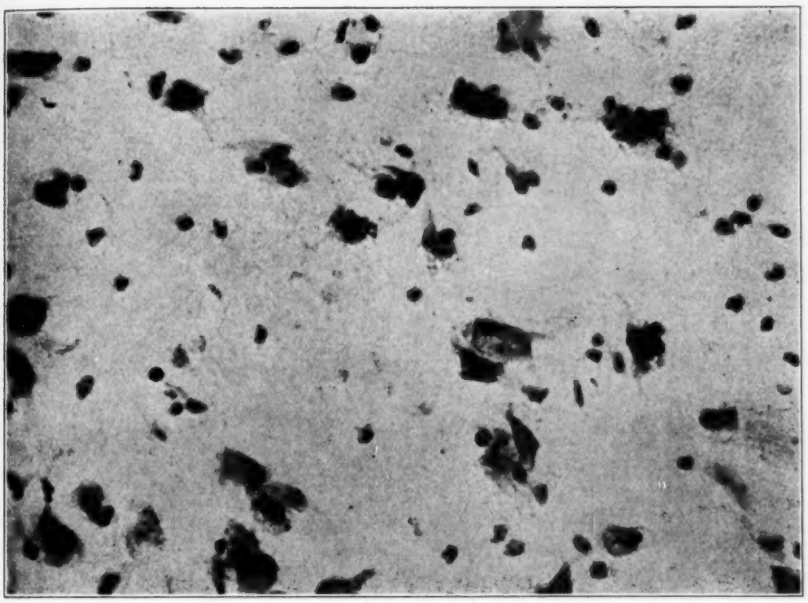

Fig. 1 (dog 1, area 8, layer VI).—Neuronophagia; eroded outlines of cells.

In outlining the cytoarchitectonic areas, we employed the map of the dog's brain which was made by Gurevich and Bychovskaja.

Results.—Dog 1.—This animal, aged 4 months and weighing 6 Kg., was killed seventeen days after removal of the left frontal lobe. At autopsy it was established that the entire frontal lobe had been removed up to the sulcus coronarius. Preparations of the right frontal lobe were studied in order to elucidate the histologic alterations resulting from removal of the contralateral frontal lobe.

Microscopic Studies: Area 8 (area frontalis anterior): No obvious alteration appeared in layers I, II and IV. In layer III degenerative changes were observed in the cells. In some cells the chromatin substance was dissolved and the outline of the cells indistinct. Neuronophagia was observed. Such alterations were more frequently seen in layers V and VI than in layer III (fig. 1).

Area 12 (area frontalis inferior): This area did not show any obvious alterations.

Area 6 (area frontalis posterior): In layer III there were numerous cells with rarefied protoplasm, irregularly and poorly stained Nissl substance and eccentric and irregular nuclei. There was proliferation of the pericellular glia. Degenerated cells were more frequent in layers V and VI. Shadow cells were often seen.

Area 4 (area praecentralis gigantopyramidalis): There were no obvious pathologic changes in the cells.

Dog 2.—This animal, aged 4 months and weighing 5.5 Kg., was killed eighteen days after section of the anterior two thirds of the corpus callosum.

Microscopic Studies: Area 8: The cells in the first two layers were intact. In layer III degenerated cells were often seen. Neuronophagia was observed. Layer IV was not altered. In layers V and VI degenerated cells with vacuolated

Fig. 2 (dog 2, area 8, layer V).—Fragmentation of processes, degeneration of cells, vacuolation and neuronophagia.

protoplasm, eroded outlines and fragmented processes were seen. Proliferation of the pericellular glia was also observed (fig. 2).

Area 6: In layers V and VI there was observed cell degeneration with neuronophagia, and in layer III there were alterations of the same character, but less pronounced.

Area 4: In layers I and II of this area there were no pathologic alterations. In layer III distinct destructive cell alterations were not often seen. The cells were mostly swollen and pale, with homogeneous structure of the protoplasm. The glial reaction was pronounced. In layers V and VI the alterations in the cells were more pronounced.

Dog 3.—This animal, aged 4½ months and weighing 6 Kg., was killed sixteen days after section through almost the whole of the corpus callosum except the splenium.

Microscopic Studies: Area 8: There were no alterations in layers I and II. In layer III there were destructive changes in the cells, the degenerated cells lying in groups. In layer IV there were no alterations.

Area 12: There were no alterations.

Area 6: Layers V and VI showed pronounced changes (fig. 3). The protoplasm of many of the cells was extensively destroyed, leaving only a nucleus encircled with glia (*Trabantzellen*). In some cells the half-destroyed protoplasm consisted of vacuoles and had a foamy structure. In layer III the pathologic changes in the cells were seen in discrete areas and were less pronounced than in the inferior layers.

Area 4: In this field layers III, V and VI showed reactive changes (slight hyperplasia) in the glia. The outlines of the nerve cells were sometimes eroded;

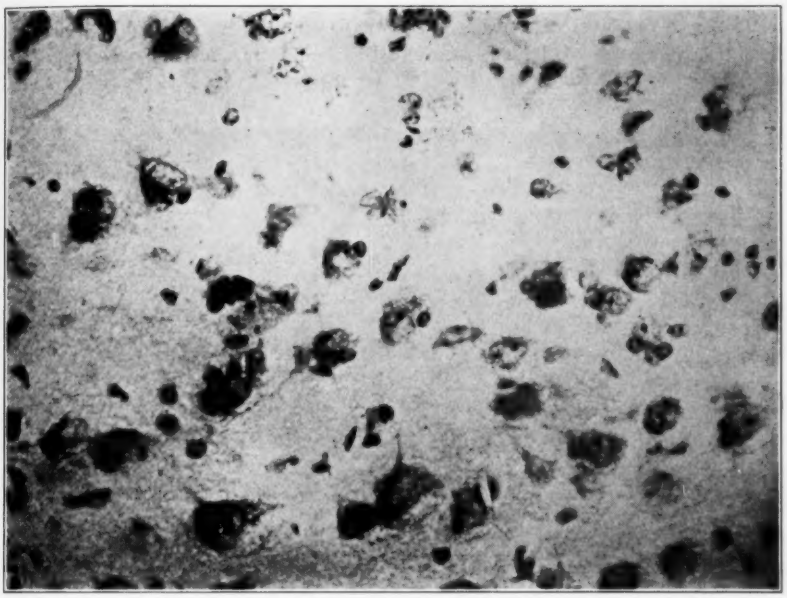

Fig. 3 (dog 3, area 6, layers V and VI).—Pronounced neuronophagia.

the protoplasm was rarefied and pale; the processes were fragmented. In layer V the Betz cells were not injured.

Dog 4.—This animal, aged 3 months, was killed eighteen days after section of the anterior part of the corpus callosum. At autopsy it was seen that the section extended to the splenium.

Microscopic Study: This yielded the same results as in the 3 other dogs. In areas 4, 6 and 8 there were pathologic changes of the cells in layers III, V and VI. In area 12 there were no alterations.

Dog 5.—This animal, aged 3½ months and weighing 4.5 Kg., was killed seven days after the operation. Autopsy showed that the posterior part of the corpus callosum, including the splenium, had been sectioned.

Microscopic Studies: The same frontal fields were studied as in the preceding dogs. Only in area 4 could distinct pathologic alterations of the cells be observed in layers V and VI. The Betz cells were not changed.

PATHOLOGICOANATOMIC OBSERVATIONS

Since in the literature we could find no positive information on the origin of the fibers of the human corpus callosum, we used human pathologic material to determine which cells and cortical layers give rise to these fibers in man. Brains in which tumors or softening had destroyed definite cortical regions of one hemisphere were used, and the changes in the corresponding architectonic fields of the contralateral hemisphere were studied.

CASE 1.—R. had a tumor of the left gyrus angularis (fig. 4). The cortex of the left inferior parietal lobe had been destroyed by the neoplasm. The tumor began caudal to the posterior ascending branch of the fissura Sylvii and extended posteriorly to the level of the sulcus occipitalis transversus. Dorsally the tumor extended to the sulci of Jensen, which in this hemisphere were short. Ventrally the tumor included part of the posterior portions of the first and second temporal

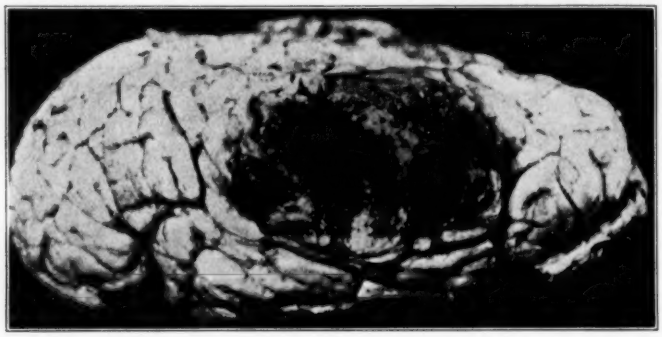

Fig. 4 (R., case 1).—Tumor of the gyrus angularis, involving area 39 and parts of areas 22, 40 and 42.

convolutions. Thus, the tumor was located mostly in the region of the angular convolution. The destruction corresponded with field 39 of Brodmann, but involved also to some extent fields 22, 42 and 40.

Histologic Studies.—In the contralateral hemisphere the most marked alterations were observed in Brodmann's field 39. Slight changes were observed in the posterior parts of fields 22 and 42. In field 39 the most pronounced cellular alterations were in layers VI (VI b) and V (fig. 5). They were less pronounced in layer III (III c); in this layer only a few cells were altered, and normal cells were seen near pathologic cells.

In field 22 less pronounced cell changes were observed—especially in layers V and VI—degenerative changes that were accompanied by neuronophagia. In layer III there were some shadow cells with neuronophagia.

CASE 2.—In the case of W., aged 39, a tumor occupied all the anterior part of the gyrus supramarginalis and the middle portion of the posterior central convolution. It destroyed the middle regions of fields 1, 2 and 3 and part of field 40 of Brodmann.

Histologic Studies.—On microscopic examination the corresponding fields of the contralateral hemisphere showed pathologic changes. The alterations were located

in layers III, V and VI. In field 1 slight hyperplasia of the glia was observed, glia nuclei being situated along the processes and on the surface of the cells. Sometimes there was erosion of the outlines of the cells. More pronounced alterations were observed in field 2. In layer III c of this field pale cells were penetrated by glia nuclei. Both true and false neuronophagia was observed. The degenerated cells were often disposed in groups. In layer VI a could also be seen hyperplasia of the glia cells on the surface of the nerve cells.

CASE 3.—K., aged 50, had softening of the right parieto-occipital region. The area of softening occupied chiefly fields 7, 18, 19 and 39 of Brodmann.

Histologic Studies.—In sections of the corresponding fields of the contralateral hemisphere pronounced pathologic changes were observed in layers III, V and VI. In field 19 changes were observed in the same three layers, but were less marked

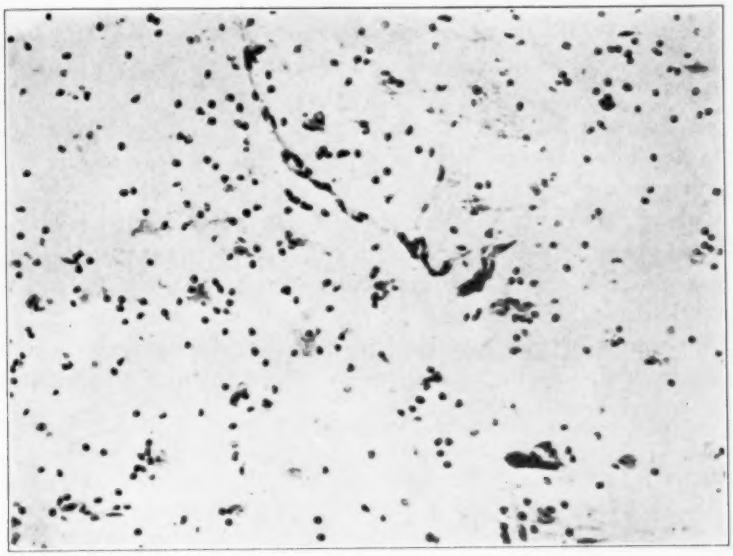

Fig. 5 (R., case 1).—Cell degeneration and neuronophagia in the right gyrus angularis, area 39, layer VI.

in layer III than in layers V and VI. In field 18 there was pronounced degeneration of cells, with neuronophagia in layers III and VI and less pronounced alterations in layer V.

CASE 4.—In the case of P., aged 53, a glioma in the first and second left frontal convolutions diffusely infiltrated the white substance and approached the cortex. The neoplasm involved the region of the centrum semiovale and the corona radiata, infiltrated the genu of the corpus callosum and penetrated the white substance of the central convolutions. The overlying cortex belonged to fields 6 and 8 of Brodmann.

Histologic Studies.—In sections of the corresponding fields of the contralateral hemisphere degenerative alterations were observed. In field 8 the changes were chiefly in layers III and V, and rarely in layer VI.

SUMMARY AND CONCLUSIONS

In order to identify the cells of origin of the fibers of the corpus callosum, the retrograde cell changes in fields 4, 6, 8 and 12 of the frontal cortex were studied after destruction of the contralateral frontal lobe in 1 dog, section of the anterior two thirds of the corpus callosum in 3 dogs and section of the posterior two thirds of the corpus callosum in another dog. There were also studied the pathologic changes in human brains with lesions in the occipital, parietal, central, frontal and temporal lobes, involving fields 1, 2, 3, 6, 7, 8, 18, 19, 22, 39, 40 and 42.

In the experimental as well as in the human pathologic material there were observed in the corresponding fields of the contralateral hemisphere pronounced pathologic changes in layers III, V and VI, except in field 12, in which no alterations were seen. After section of the corpus callosum analogous alterations were observed in the fields of the two hemispheres. The cells of origin of the fibers of the corpus callosum lie in layers III, V and VI. The last two layers of the cortex must be considered as giving origin not only to efferent but also to efferent commissural fibers.

Only a part of the cells of these layers were affected. The commissural fibers do not all arise from one layer, and their cells of origin in layers III, V and VI are intermingled with cells which have other connections.

The results of this investigation show that the homotopic fields are always injured. Further investigation will be required to elucidate the question of heterotopic connections.

DIFFUSE PROGRESSIVE LEUKODYSTROPHY IN THE ADULT

WITH PRODUCTION OF METACHROMATIC DEGENERATIVE PRODUCTS (ALZHEIMER-BARONCINI)

LUDO VAN BOGAERT, M.D.
AND
ANDRÉ DEWULF, M.D.
ANTWERP, BELGIUM

The observation which we record here concerns a case of diffuse leukodystrophy beginning in an adolescent and progressing for seventeen years clinically as pseudoparalytic dementia, with the addition of double athetosis and intense spasms of contracture. From the anatomic point of view this condition is indistinguishable from the familial forms of the disease. The brother of our patient was well, but we have no information concerning other members of his family. We cannot be certain, therefore, that his disease was not of the heredofamilial type. The presence of metachromatic degenerative products is another peculiarity of this case, and we shall return later to the particular value which Einarson and van Neel [1] accorded them, as described in their recent monograph.

REPORT OF A CASE

History.—F. W., a man aged 38, concerning whom information was given by his family on May 19, 1937, had one brother who was well; no information concerning the family antecedents was obtained. No incident of nervous disorder during the patient's infancy is known. He did his schoolwork well and seemed normal until he fell from a horse, at the age of 21, while doing military service. A few months later he began to drink heavily, without, however, becoming really drunk. He had ideas of grandeur, thought he was going to become an ambassador and gave himself honorary titles, although still working as a clerk. His handwriting became illegible and irregular. His intellectual faculties began to fail markedly; he was discharged from his employment two years after the fall from the horse and remained for three years with his family. During this time his behavior was abnormally childish; he went into the streets in his

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Read at the meeting of the British Neurological Society, Antwerp, Belgium, on May 7, 1938.

From the Laboratory of Neuropathology of Bunge Institut (Antwerp), and the Institut St. Camille (Corbeek-Loo).

1. Einarson, L., and van Neel, A.: Beiträge zur Kenntnis sklerosierender Entmarkungsprozess im Gehirn, mit besonderer Berücksichtigung der diffusen Sklerose, Acta jutland. **10**:2-48, 1938.

shirt-sleeves, proposed to passers-by that they box with him and wanted always to try who was the stronger; he did not go beyond verbal proposals, however, and committed no antisocial acts. At home he was affectionate, except that toward the end of the period he occasionally showed hatred toward his foster mother. He could no longer read newspapers, but rested for hours on a chair immobile. This state of depression lasted for weeks; then for a time he would be abnormally exuberant. He was disoriented for time and place.

A tremor of the whole body, difficulty in walking, an abnormal attitude of the right foot, which turned inward, and paresis of the right leg, all appeared a little later, but he was still able to walk about. He never had epileptiform attacks or any fits of anger. He was rather clumsy in all actions, but managed to feed himself and did not need to be aided in any way.

Aggravation of his mental symptoms necessitated commitment to the Institut St. Camille, at Bierbeek, on Sept. 21, 1932.

Examination.—On May 5, 1937, the patient was taciturn, and spoke rarely, in disconnected, brief phrases. His face was usually expressionless, but sometimes expressed fear.

When he was lying in bed the attitude of the lower limbs was peculiar—the right upper extremity was extended, and the right foot was in plantar flexion and turned strongly inward; the left lower extremity was slightly flexed at all joints, and there was slight inward rotation of the left foot. The left thigh was adducted to such an extent that it was crossed over the right thigh. From time to time the right thigh would be similarly crossed over the left. When passive movements were made of the lower extremities the patient opposed them voluntarily. At times forced flexion of one lower extremity was accompanied by spontaneous flexion of the other. The upper extremities had no special abnormal position. The patient moved them voluntarily in all directions and opposed passive movements. Occasionally forced passive movements of the upper extremities were accompanied by spontaneous movements of the lower limbs.

From time to time there occurred strong involuntary contractions of all the muscles of the body—purposeless, incoordinate and spasmodic. One saw them particularly well when the patient changed his lower limbs in the crossed position. Involuntary movements of flexion and extension of the lower extremities were accompanied by generalized spasms; the attitude of the hands at these times was athetotic. The spasms were not accompanied by tremor. At rest the muscles were sometimes tense, sometimes flaccid. When the patient extended his fingers, some were hyperextended in disharmonious attitudes. The movements were also slightly irregular, with a rhythm much slower than that of a parkinsonian tremor. When the patient was held upright the hyperextension of the lower limbs reminded one of a decerebrate attitude, but the equinovarus was less marked.

Examination of the reflexes was difficult because of the incomprehension of the patient. There was a Babinski sign on both sides, more marked on the right. The tendon reflexes did not seem much exaggerated. The cremaster reflexes were present. The abdominal reflexes were difficult to obtain. The pupils reacted feebly to light; they were approximately equal. There was no spontaneous nystagmus.

The patient could not be brought to execute the movements necessary in testing for cerebellar disturbances. There was no special muscular atrophy, but emaciation was marked.

At times the patient laughed or cried spasmodically without cause. He made no outcry. There was no goiter or exophthalmos. He was almost completely demented.

Laboratory Examinations.—There was no albumin or sugar in the urine. The spinal fluid was normal; the Pandy and the Bordet-Wassermann reactions were negative. The Wassermann reaction of the blood was also negative.

Course.—The patient died on May 19, 1937.

Summary.—The illness began with a fall, at the age of 21. Shortly afterward there appeared drunkenness, delusions of grandeur, tremor and difficulty in writing and walking. After alternating periods of depression and excitation, the patient was committed to an institution, diagnosis being grave organic dementia. The facies was expressionless, and there were spasmodic paraplegia, paroxysmal generalized contractures with abnormal athetotic attitudes of the upper limbs and a Babinski sign bilaterally. The serologic reactions were negative. The illness lasted seventeen years.

The disease in this case belongs to the adult type of leukodystrophy (Ferraro [2]), concerning which one of us (L. v. B.), in collaboration with Nyssen,[3] has published a previous study, but it represents a sporadic form of particularly slow evolution (seventeen years). There were here the same psychic symptoms, characterized at first by affective disturbances and evolving rapidly toward grave dementia without remission. One observed a syndrome of spasmodic paraplegia with rigidity in extension, loss of mimetic and static automatic movements, anarthria and, in the final stage, paraplegia in flexion. We have no valid information concerning the state of the visual function.

The patient's absurd delusions of grandeur in this case resembled the observations on adults reported by Alzheimer [4] (originally by Baroncini), Nissl,[5] Witte [6] and Kaltenbach,[7] in which "paralytic" delirium was noted. The disease resembled the juvenile form because of its athetotic component.

The clinical diagnosis of such a disturbance is always difficult. Without doubt, predominance of the psychic symptoms detailed by Guttmann, who insisted on the exogenous reactions of Bonhoeffer,

2. Ferraro, A.: Familiar form of Encephalitis periaxialis diffusa, J. Nerv. & Ment. Dis. **66**:329, 1927.

3. van Bogaert, L., and Nyssen, R.: Le type tardif de la leucodystrophie progressive familiale, Rev. neurol. **65**:21-45, 1936.

4. Alzheimer, A.: Beiträge zur Kenntnis der pathologischen Neuroglia und ihrer Beziehungen zu den Abbauvorgängen im Nervengewebe, in Nissl, F., and Alzheimer, A.: Histologische und pathologische Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1910, vol. 3, pp. 401-562.

5. Nissl, F.: Nervensystem, in Ehrlich, P.; Krause, R.; Mosse, M.; Rosin, H., and Weigert, K.: Enzyklopädie der mikroskopischen Technik, Berlin, Urban & Schwarzenberg, 1910, vol. 2, pp. 284-342.

6. Witte, F.: Ueber pathologische Abbauvorgänge im Zentralnervensystem, München. med. Wchnschr. **68**:69-82, 1921.

7. Kaltenbach, H.: Ueber einen eigenartigen Markprozess mit metachromatischen Abbauprodukten bei einem paralyseähnlichen Krankheitsbild, Ztschr. f. d. ges. Neurol. u. Psychiat. **75**:138-146, 1922.

associated with an epileptic and progressively spasmodic syndrome, is of real value. Cortical blindness, with or without hemianopia, is another significant sign, but is absent in many cases (Bouman [8]). In spite of the rarity of the condition, we believe one should think of such a disease in the presence of the following signs: progressive evolution toward grave dementia without remissions; rapid passage from disturbances in speech to anarthria; aggravation of the disturbance in walking, which, after having been cerebelloataxic, becomes rapidly impossible, and the terminal appearance of quadriplegic rigidity with contracture and an athetotic component.

Histologic Observations.—Histologic study of this case concerned especially the extent of the pathologic process and its mode of disintegration and reparation.

1. Topography of Lesions of the Myelin and Neuroglia: One hemisphere was cut in verticotransverse series and stained by the Nissl, Weigert-Pal, Spielmeyer and Holzer methods and with scarlet red. The other was utilized for various technics: scarlet red, sudan red, sudan black (Lison and Dagnelie [9]) and the methods of Smith and Dietrich, Bielschowsky, Reumont and Smith and Lorrain.

The most anterior section passed in front of the corpus callosum and the anterior extremity of the lateral ventricle. The demyelination here affected the entire oval center, but was not complete. The coloration was spotty, except for the U fibers, which were everywhere conserved.

The next section passed through the head of the caudate nucleus and the anterior part of the internal capsule. There was a certain degree of hydrocephalus, due to retraction of the ventricular walls. The caudate nucleus and the anterior part of the lenticular nucleus were of normal appearance, but the corpus callosum was reduced to a quarter of its normal thickness. The septum pellucidum was thin, and the fibers of the trigon were scarcely recognizable. Homogeneous demyelination here affected all the oval center, including the prolongation of the anterior parietal region and the part of the temporal lobe present. The arcuate fibers and the axis of the third frontal convolution seemed less profoundly demyelinated. The U fibers were everywhere conserved, although they were less dense than areas beneath the second and third frontal and prefrontal convolutions. The anterior part of the internal capsule seemed almost intact.

A third section passed through the basal ganglia. These areas were condensed and shrunken, but the posterior part of the internal capsule seemed unaffected. The thalamus, the globus pallidus, the lenticular nucleus, the columns of the fornix and the optic tracts were well preserved. A lighter patch appeared where the corona radiata commences to expand on emerging from the internal capsule. The demyelination of the oval center was again marked; it reached even to the immediate neighborhood of the ventricular wall. The corpus callosum was reduced to one-fifth its normal thickness. The arcuate tract was also affected. In the white axis of the prefrontal and anterior parietal regions, as well as in the inferior frontal and limbic convolutions, a certain number of fibers were conserved.

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8. Bouman, L.: Diffuse Sclerosis: Encephalitis Periaxialis Diffusa, Bristol, England, John Wright & Sons, Ltd., 1934, p. 120.

9. Lison, L., and Dagnelie, J.: Méthodes nouvelles de coloration de la myéline, Bull. d'histol. appliq. à la physiol. **12**:85-91, 1935.

In the oval center the disappearance of the myelin gave numerous areas a spongy appearance. The anterior and external nuclei of the thalamus were proportionately more atrophied than the pallidum and lenticular nucleus.

A fourth section, through the center of the basal ganglia and the internal capsule, showed partial demyelination of the middle third of the capsule and atrophy of the thalamus. The putamen and pallidum were small, but had the normal myelination.

The fifth section passed through the posterior third of the posterior horn of the lateral ventricle. The ventricle was enlarged. The optic radiations and tapetum were relatively well conserved, and were in contrast with the paleness of the corona radiata. The U fibers were conserved, but were less well impregnated, and in general the white substance was much diminished in volume.

A section passing through the most caudal part of the occipital lobe, including the calcarine fissure, showed the same atrophy of the white substance except that of the superior parietal convolution, which was relatively well preserved.

A section through the locus niger and rubrothalamic region showed the foot of the peduncle to be completely intact. Only the geniculate bodies seemed slightly less myelinated than usual. The radiations of the tegmentum seemed normally dense. The upper part of the protuberance showed nothing remarkable except questionable paleness of the pyramidal tracts. The transverse fibers of the pons were slightly paler than normal. In the bulb, the olivary regions and the pyramidal tracts seemed intact. The dentate nuclei and the white matter of the cerebellum were normal.

The optic nerve showed no discernible abnormalities. Sections of the cervical and upper dorsal regions of the cord showed slight marginal paleness and slight pallor of the crossed pyramidal tracts and of the juxtamedian territory of the posterior third of the columns of Goll. The same lesions were present, but were scarcely visible in the middle and inferior dorsal regions of the cord. They could not be seen in the lumbar region.

In large sections through the frontal pole stained by the method of Holzer one saw the spotty appearance in the region of the ventricles even better than in the Pal-Weigert preparations (fig. 1 *A*). In the occipital region the spotty sclerosis was less regular because of the atrophy of the entire lobe (fig. 1 *B*). It extended, nevertheless, into the interior of the superior parietal and angular convolutions, that is, where the Pal-Weigert preparations showed no lesions. A Holzer preparation corresponding to the third Pal-Weigert section confirmed the density of the sclerosis of the oval center and corpus callosum in this region. One saw, moreover, definite gliosis in the middle third of the internal capsule, throughout the optic tract and in the stratum zonale, the anterior medullary lamina, the external medullary lamina and, to a lesser degree, the internal medullary lamina of the thalamus. This gliosis was dense beneath the ependyma in the substantia grisea around the third ventricle and in the taenia thalami.

The next section showed gliosis of the median third of the internal capsule, corresponding to the pyramidal tract, and slight gliosis of the anterior limb. A section passing through the substantia nigra and the red nucleus showed marginal gliosis of the peduncle and diffuse gliosis of the internal nucleus of the thalamus, the median center and the semilunar nucleus of the external geniculate body. The optic tract had marginal gliosis, especially in its most ventral part; the center was less involved. Gliosis of the same order involved the entire surface of the peduncle and penetrated it for about one fifth of its thickness. The locus niger was normal. The protuberance seemed intact. Sections of the bulb showed only

a slight degree of olivary and subpial gliosis. The pyramidal tracts were slightly darker than normal, but one did not see definite gliosis. Sections of both optic nerves showed a moderate degree of interfascicular gliosis. Sections of the cervical, dorsal and lumbar portions of the cord showed no evidence of gliosis.

The process of demyelination had, therefore, involved the entire oval center. It had respected the cerebellar white matter and the myelin sheaths within the basal ganglia, but touched the internal capsule, which was slightly less myelinated in its middle third. There was no typical secondary degeneration in the cerebral peduncle, but the pyramidal fibers at the level of the pons on one side possibly were slightly involved. Degeneration was not visible in the bulbar portion of the pyramidal tracts, and was scarcely discernible at the various levels of the cord. The slight pallor of the posterior columns was of doubtful significance. The basal ganglia

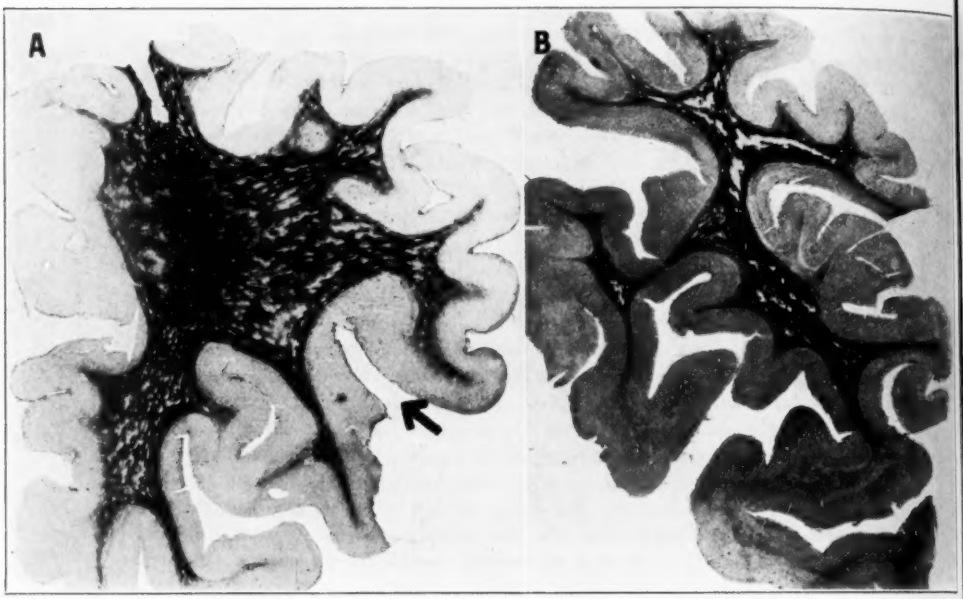

Fig. 1.—*A*, section of the prefrontal region, showing dense and spotty gliosis of the oval center. The arrow indicates an artefact. *B*, section of the occipital pole, showing generalized gliosis of the white matter. Holzer's method.

and the thalamus were considerably reduced in volume. The oval center was the seat of dense, isomorphous gliosis, of spotty aspect, which extended into the anterior limb of the internal capsule and the medullary laminas of the thalamus. There was probably abnormal gliosis of the thalamus. On the other hand, gliosis was absent in the pyramidal segment of the foot of the peduncle and in the protuberance, but was present to slight extent in the bulbar portion of the pyramids and the olives. The walls of the third ventricle and the optic tracts showed a moderate degree of marginal gliosis. The gliosis of the oval center was especially dense; it constituted an independent process, in contrast to the slight gliosis of the optic thalamus.

2. Cellular and Axonal Lesions: In myelin preparations we noted the disappearance of the tangential fibers of the cortex, superficial as well as deep, remarked on in a previous publication by one of us (L. v. B.) and Scholz.[10] The atrophy of the optic thalamus was accompanied by marked rarefaction of the intrathalamic fibrillary systems, but the fiber systems of the basal ganglia were well conserved. We did not see any cellular lesions of the cortex, in spite of careful examination. The Betz cells and the cells of the third layer were everywhere conserved. This cellular integrity of the cortex was confirmed by Cajal preparations. The axons, when impregnated by Bielschowsky's method, presented the classic lesions; some of them, nevertheless, were preserved.

3. Blood Vessels: In rare areas there was slight perivascular infiltration with lymphocytes within the space of Virchow and Robin, and outside it were many macrophages. Proliferation of connective tissue, either diffuse or confined to the adventitial walls, was not demonstrated by the method of Achúcarro, as in the recent observations of King.[11]

4. Formula of Disintegration: The demyelinated zones were cluttered with an abundance of macrophages filled with granules, which were often distributed along the fibers or bundles of fibers. These cells stained a deep violet red with thionine, and so were visible at low magnification.

The compound granular corpuscles did not stain brilliantly with scarlet red, but with this dye and with sudan red they stained a dull rose. Nowhere could any neutral fat be found. With nile blue these cells usually took a deep blue, never a reddish, stain. They stained grayish black with sudan black, did not stain by the method of Smith and Dietrich and stained only slightly with hematoxylin. A certain number were observed near the vessels, but this was not the rule. They were seen also in regions where gross alterations of the fibers were not yet disclosed by methods for myelin, for example, in the dentate nucleus, the cerebellar white substance, the foot of the peduncle and the posterior columns of the spinal cord. They were numerous in the internal capsule, the ansa lenticularis, the zona incerta, the bundle of Vicq d'Azyr and the secondary degenerations of the pyramidal tracts. The cells of the locus niger, the compact hypothalamic formations, the semilunar nucleus of Flechsig, the innominate substance of Reichert, the body of Luys and the pallidum, all presented frequently metachromasia of their lipochrome substance.

The compound granular corpuscles were most clearly seen in sections stained with cresyl violet; here they stood out against the background of the preparation by virtue of their size and their dark violet color. They were to be observed throughout the extent of the affected areas, but not beyond the band of U fibers. Sometimes the entire cell was dark and had a uniform violet-black color; at other times one could recognize distinctly a granular structure, coalescence of the particles producing a single globule. In thin preparations one could follow the formation of such globules. The beginning consisted of the appearance of fine, dark violet granules in the protoplasmic mass (fig. 2 *A*). These increased in number and finally occupied the entire cell body. The latter frequently had a glossy appearance. In the same section one might see granular cells in different stages of metachromatic

10. van Bogaert, L., and Scholz, W.: Klinischer, genealogischer und pathologisch-anatomischer Beitrag zur Kenntnis der familiären diffusen Sklerose (familiäre juvenile Leukodystrophie–Familie Ros.), Ztschr. f. d. ges. Neurol. u. Psychiat. **141**:510-541, 1932.

11. King, L. S.: Connective Tissue Reaction in Multiple and in Diffuse Sclerosis, Arch. Path. **23**:338-349 (March) 1937.

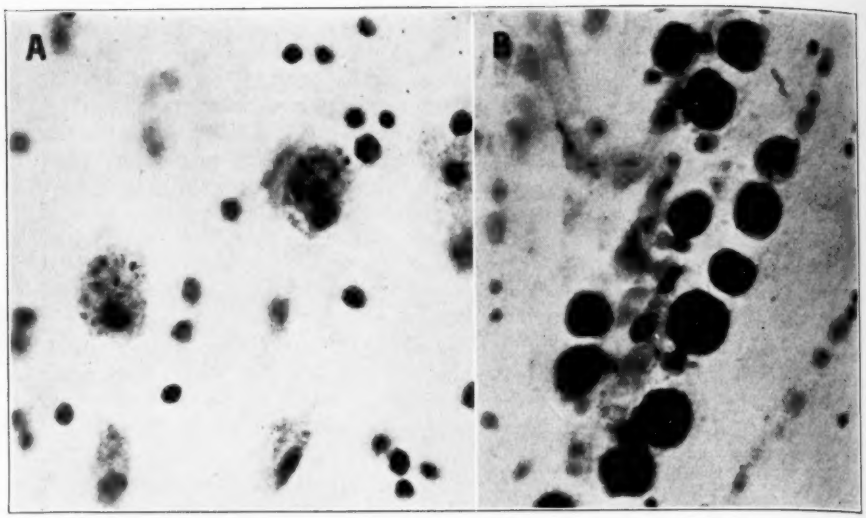

Fig. 2.—*A*, first stage in the formation of granular cells with metachromatic tinctorial reactions. Deep violet granules appear in the cytoplasm. *B*, granular corpuscles in the pericapillary region in a different stage of metachromatic evolution than that shown in *A*. Nissl's method.

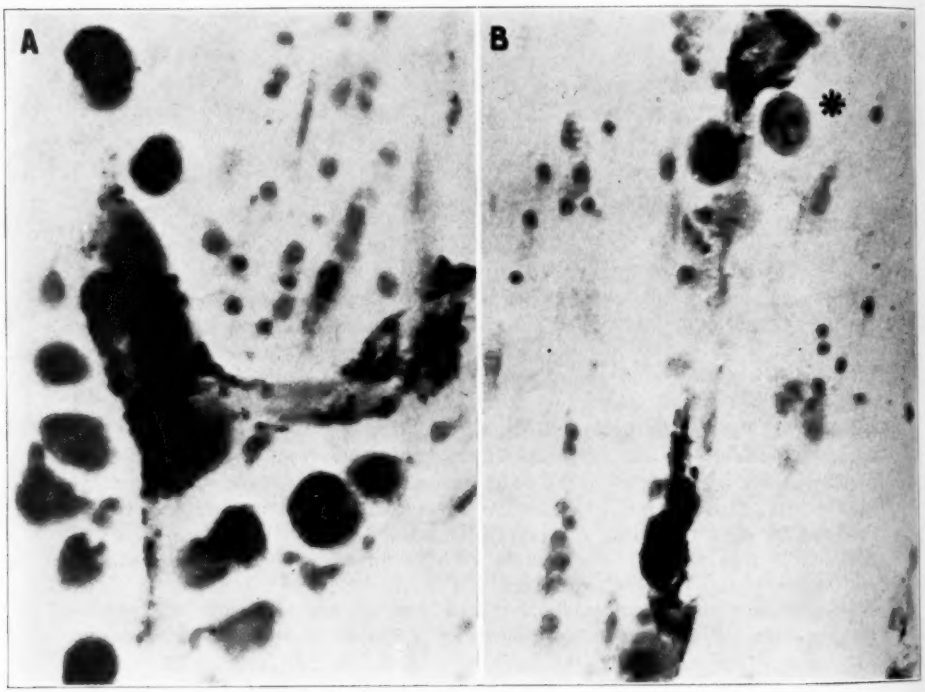

Fig. 3.—In *A* the adventitial cells themselves, and in *B* the endothelial cells of the capillaries, contain metachromatic granules. At the point indicated by an asterisk, one notes a cell the center of which is occupied by a rosary of metachromatic granules in the process of diffusion. Nissl's method.

evolution. As the granular cells became pigmented, the degenerative substance little by little lost its granular character, and the entire globule progressively took the violet stain (fig. 2 *B*). The appearance of small black granules constituted the initial stage of metachromasia. In the region of abundant metachromatic disintegration one could see the granules in adventitial cells (fig. 3 *A*); even the endothelial cells of capillaries (fig. 3 *B*) presented the same metachromatic granulations.

Nissl preparations showed, besides the uniformly stained globules, granulations scattered throughout the section and staining various shades of blue. In preparations stained by the method of Azan and Heidenhain the granular cells of the white substance differed in appearance according to whether they were situated in the center or in a band of U fibers. In the latter they were granulated and brilliant red; in the center, on the contrary, they had a more or less pale blue-violet aspect with rare brilliant red inclusions. In sections stained by Spielmeyer's method the granular cells were a dirty, dull yellow in the clearer regions and a smokier yellow in the bands of U fibers.

COMMENT

In cases like the one described here, the myelin material which is disintegrated and free in the tissue is not as abundant as that observed in the cases reported by one of us in collaboration with Scholz and with Bertrand.[12] Besides the granular cells, one does not see many fatty granulations dispersed in the surrounding tissue (fig. 4 *A*), but the same incapacity of the neuroglia cells to transform the disintegrating substances completely into neutral fat is again evident.

The metachromatic products are seen in regions of the white substance where degeneration of the myelin is still invisible and where the reactive gliosis has not yet made its appearance. It is true that these products are found in such regions in small quantities. There is a certain relation between the intensity of the disintegration in process and the quality of the metachromatic products, but not between the latter and the demyelination.

In the corpus callosum and in the oval center the sheaths of vessels contain both inflammatory cells and metachromatic granular cells (fig. 4 *B*). One is astonished to find in the same slow process such a great number of granular cells in the neighborhood of the vessels, but outside the perivascular spaces, and such dense gliosis. On the contrary, in the case of B., one of diffuse sclerosis in an adult, reported with Nyssen,[3] the granular cells were rare and were seen only in the periphery of the lesions, and not in the central parts of the oval center. In the present case the globoid granular cells were seen even in the subependymal region about the third ventricle. The metachromatic products described in this case did not exist in the case of B., nor in any other of the cases of familial type which we have reported before.

12. van Bogaert, L., and Bertrand, I.: Les leucodystrophies progressives familiales, Rev. neurol. **2**:249-286, 1933.

We observed the same granular products in the endothelial cells of the vessels as in the compound granular corpuscles (fig. 3 *A* and *B*). Granulations staining with hematoxylin have been described in the same regions by Bielschowsy and Henneberg.[13] These authors observed also gross formations containing granular products in the zones not yet demyelinated. The ganglion cells surcharged with lipochrome have a tendency (as we have noted in the zona incerta, the locus niger, the body of Luys and the optic thalamus) to take on the same metachromatic appearance, and that aside from diffuse sclerosis.[14]

These metachromatic substances were reported on at the same time by Nissl and by Alzheimer. Nissl[5] described them in nerve and glia cells in a case of

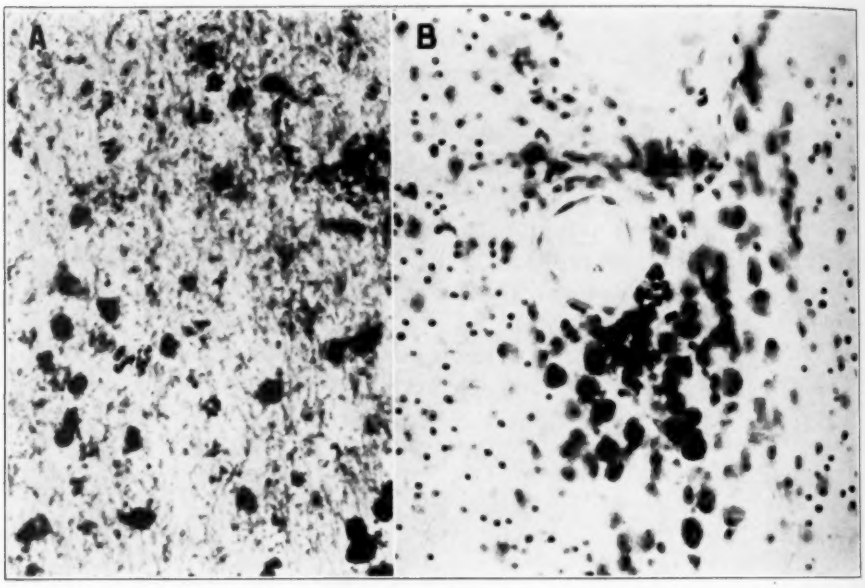

Fig. 4.—(*A*) Outside the granular cells the metachromatic granulation is dispersed in the ground substance. Nile blue stain. (*B*)At the same time, around a vessel in the oval center are an adventitial reaction, an accumulation of granular cells, a part of which are metachromatic, and recent macroglial reaction. Nissl's method.

diffuse sclerosis. "They appear," he said, "in the form of granules of varying size in frozen sections of formaldehyde-fixed material, and stain a bright red with toluidine blue or polychrome blue." It was remarked also by Alzheimer[4] and Baroncini that they had a metachromatic tint with basic aniline dyes. Witte,[6] in a case of diffuse sclerosis, observed this substance filling the glia cells in

13. Bielschowsky, M., and Henneberg, R.: Ueber familiäre diffuse Sklerose (Leukodystrophia cerebri progressiva hereditaria), J. f. Psychol. u. Neurol. **36:** 131-181, 1928.

14. Scholz, W.: Personal communication to the authors.

the form of granules of uniform size, closely packed together even in the processes. Between them and the heavily laden gliogenous compound granular cells were all stages of transition. Witte expressed the belief that this granular product arises by destruction of the myelin, but since he noted it also in the hypophysis, the kidneys, the testes, the epithelium of the urinary tubules and the liver, finding even metachromatic renal casts, he concluded that the disorder in the nervous system and that in other organs were identical, i. e., a disturbance of metabolism. In the case of Kaltenbach [7] the granules stained bluish red with toluidine blue and followed the course of the myelinated fibers. Outside the corpuscles Kaltenbach recognized other metachromatic granules oriented in parallel lines along the fibers. They were rare in the cortex. Only a part stained with scarlet red or sudan red. They stained red in hematoxylin and eosin preparations. He did not see them in the hypophysis, the epiphysis or the choroid plexus. The corpuscles described by Kaltenbach differ from those described by Bouman.[15] Bouman described numerous blocks of pigment situated in the deepest layers of the cortex, of a brownish green color, consisting of fine granulations, which could be seen also in the subcortical layers and in the U fibers. A great number of similar droplets were even enclosed in the ganglion cells. We believe that the formations described by Bouman are not similar to those described by Kaltenbach. However, again, Jakob [16] gave a suggestive description of these products of disintegration in a case of diffuse sclerosis. The color in his case varied from red to violet, with special degeneration of the white substance rather than diffuse sclerosis. To this series of cases (we do not know whether the case of Nissl is different from that of Alzheimer and Baroncini), reported by Alzheimer, Witte and Kaltenbach, in which the process was generalized and presented the same pseudoparalytic picture (plus cerebellospasmodic signs in the case of Kaltenbach), Einarson and van Neel [1] added an observation by Carillo [17] and their own case 1, in which similar masses of metachromatic substances were present. The process in the cases of Carillo and Einarson and van Neel had, however, a pseudoneoplastic evolution with the development, in the case of Einarson and van Neel, of choked disks. In Carillo's case the lesion was situated bilaterally in the central parietal region, with atrophy of the postcentral convolutions. This lesion was especially prominent in the left hemisphere, in which were observed substitutive gliosis, gross perivascular reactions with pericapillary hemorrhages and proliferation of the vessels, which had in places an angiomatous appearance. This participation of the mesenchyme was invoked by Carillo to justify inclusion of his case in the group of inflammatory sclerosis. In case 1 of Einarson and van Neel the evolution was extraordinarily slow (twenty-two years), with periods of remission and symptoms of parieto-occipital involvement and intracranial hypertension. There were confluent foci in the white substance of the occipitotemporal and posterior parietal areas, especially in the right hemisphere, and in one cerebellar hemisphere a cystic cavity, around which were foci of degeneration. Gliosis was unimportant in their case. Proliferation of capillaries was observed in the deepest cortical layers and near the cystic cavity in the cerebellum.

From the clinical as well as the anatomic point of view, it is difficult to include the cases of Carillo and of Einarson and van Neel in the same category with those

15. Bouman, L.: Encephalitis Periaxialis Diffusa, Brain **47**:453-488, 1924.

16. Jakob, A.: Anatomie und Histologie der Grosshirnrinde, Vienna, Franz Deuticke, 1927, p. 97.

17. Carillo, R.: Sklerosierend-atrophische Encephalitis der Hemisphären, Bol. Inst. clin. quiz. Univ. Buenos Aires **8**:136, 1932.

of Alzheimer and Baroncini, Witte and Kaltenbach. In the cases of Carillo and of Einarson and van Neel the metachromatic substance did not stain with scarlet red. We have already reported the tinctorial reactions in our case; the granular product was not absolutely refractory to scarlet red or sudan red but stained a dull rose. It stained also with hematoxylin lake.

Our case is most nearly similar to the cases of Alzheimer and Baroncini, Witte and Kaltenbach. Is it not strange that the picture in these cases differs from that in the cases of Carillo and Einarson and van Neel? Visceral examination in our case revealed nothing abnormal. Except for the adrenal glands, which, unfortunately, were overlooked, a series of other organs—hypophysis, thyroid, kidneys, liver, spleen, pancreas and lymphatic glands—were studied thoroughly. In none of these was any trace of metachromatic granulation revealed by thionine. For this reason, and because of the peculiar character of the initial stages of the metachromasia, we believe that the metachromatic substance represents only a particular stage in the evolution of the disintegrative products and that it is not the earmark of a disease of metabolism *sui generis,* as Alzheimer and Jakob asserted.

What is the first appearance of this alteration? In Nissl preparations examined under an oil immersion lens, the metachromatic corpuscles are at first included in vacuoles. As the compound granular corpuscles swell these punctiform inclusions become rarer. The metachromatic substance diffuses in the cell body. In general these cells have more granulations as their general tint becomes progressively darker. In the same regions one observes similar granulations in the endothelial cells of the capillaries. Between the macrophages are rare swollen macroglia cells the processes of which contain the same granulations. We have already mentioned metachromasias of ganglion cells, which cause one to ask whether a similar process has not affected the lipochrome to the point of altering its tinctorial properties in the same direction as those of the contents of the classic myelophages. This strange metachromasia of the lipochrome, reported by Witte, would thus have a new significance; not only are the glia cells insufficient for one phase of their lipolytic function, but the ganglion cells themselves present a modification in the colloidochemical composition of their lipofuscin.

We believe, however, that one should not attach too much importance to the metachromasia of the vacuoles in the ganglion cells, which can be observed in formaldehyde-fixed material in cases of other maladies than the one which we are discussing here. Nevertheless, this is not true of the metachromatic disintegration the progress of which we have here been tracing. This proceeds in the same manner as that in classic familial progressive leukodystrophy. The analogy in the mode of evolution of the pathologic process is much more important than the metachromasia of the contents of the macrophages. It is on the basis

of this analogy of structure that we classify our case with the leukodystrophies of heredodegenerative type, in spite of the absence of proof obtained from a familial history. The presence of products with special tinctorial qualities shows the close relationship to the 5 cases on the basis of which Einarson and van Neel established the group of "diffuse progressive metachromatic leukoencephalopathy," but this common denominator should not make one forget the anatomicoclinical disparity.

Two points remain to be emphasized: 1. The inconsiderable rarefaction of the myelin sheaths below and within the internal capsule is not easy to explain. Not all axons are destroyed, but that is an observation we have made in other cases in which there was, nevertheless, considerable typical secondary degeneration of the pyramidal tracts. The gliosis in these regions is dubious as seen in Holzer preparations; yet in Nissl preparations the neuroglial nuclei in the pyramidal tracts seem to be increased in number. In none of our previous cases did we find medullary lesions so slight as in this case. This fact is perhaps consistent with the slight spasticity observed clinically. Greenfield [18] has already insisted on the degeneration of the pyramidal tracts subsequent to a lesion of the white substance—a classic wallerian degeneration—in certain diffuse scleroses.

2. The glial changes in this malady have interested one of us (A. D.) especially, because anomalies in the behavior of this structure are invoked in support of certain concepts of pathogenesis. In the cortex, beside normal microglia cells are others which give signs of progressive change—augmentation in the volume of perinuclear cytoplasm and hypertrophy of the processes. One sees some rod cells and here and there moderate multiplication of microglia, but no transformation into compound granular corpuscles. The microglial reaction is, moreover, discrete and does not resemble in any way that seen in dementia paralytica. In the white substance the numerous macrophages seem to have come exclusively from the microglia. The classic transformation of the microglia into compound granular cells may be observed in all its stages. No other cellular origin seemed probable.

We used no special technic for the oligodendroglia. The sections impregnated for microglia showed that the oligodendroglia cells were swollen. This swollen clarification of these cells could be seen in the cortex as well as in the white matter. The oligodendroglia nuclei were surrounded by a clear halo, limited by a membrane. However, such appearances are banal and may be observed in many pathologic

18. Greenfield, J.: A Form of Progressive Cerebral Sclerosis in Infants Associated with Primary Degeneration of the Interfascicular Glia, in Volume jubilaire en l'honneur du Professeur G. Marinesco, Bucarest, Societé Roumaine de Neurologie, Psychiatrie et Endocrinologie, 1933, pp. 257-276.

processes unassociated with demyelination. Nothing here would permit one to assume a relation between the oligodendroglia and the demyelination. We did not observe by the use of appropriate technics the so-called mucoid degeneration (Bailey and Schaltenbrand [19]). We did not observe the transformation of astrocytes into granular corpuscles. The theoretic point of most importance in this case is that the oligodendroglia cells were not implicated. The swelling of these cells is of no importance.

The position of the disease in this case in the group of diffuse scleroses is not difficult to define. In spite of the case being an isolated one (there was a brother who was well, but a more detailed family history could not be obtained), the condition is related to the heredodegenerative group because of the predominance of the disintegrative over the proliferative and the vascular exudative process. The disintegration proceeds with striking rhythm and generalization. The presence throughout the extent of the white substance, that is, beyond the sclerosed areas, of the metabolic products of catabolism probably originating from the myelin, in the course of a disease which evolved during seventeen years, is in itself instructive. If one recalls the almost complete inertia of the vascular apparatus in the face of such disintegration, one is obliged to admit that in this disease destruction of the myelin takes place under peculiar conditions. The reparative gliosis is already advanced when the compound granular corpuscles are scattered throughout the white substance. Doubtless a certain number are already in contact with the vascular and ependymal pathways of drainage, but it is evident that they accumulate there without evolution of their tinctorial qualities toward the sudanophilic stage characteristic of classic compound granular corpuscles. The vascular wall seems to accept the metachromatic granules as they are, and in the ground substance one sees fine droplets of lipoidal substance which have not yet been absorbed. Here again, both in the granular cells and in the mesenchymal apparatus, there is the same functional incapacity to metabolize the derivatives of the myelin which we have remarked in the cases of familial type, with this difference, that the disintegration is arrested at an unusual stage in the formation of degenerative products, in which they react metachromatically to basic aniline dyes. This metachromatic particularity of the degenerative products is observed throughout the white substance, even where the demyelination is not yet visible. Such an observation is valuable, and needs no commentary.

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19. Bailey, P., and Schaltenbrand, G.: Die muköse Degeneration der Oligodendroglia, Deutsche Ztschr. f. Nervenh. **97**:231, 1927. Schaltenbrand, G.: Encephalitis Periaxialis Diffusa (Schilder), Arch. Neurol. & Psychiat. **28**:944 (Dec.) 1927.

CONCLUSION

The adult form of diffuse sclerosis may have a particularly long evolution (seventeen years in the case reported) with a clinical picture, at the same time, of pseudoparalysis and athetosis. The clinical diagnosis is always difficult. It is based on the association of mental disturbances with an epileptic, spasmodic component and a progressive cerebellar and athetotic evolution with gross disorders of speech, ending in loss of articulation.

In the case reported here the disease was characterized pathologically by a metachromatic disintegrative process. It presents, otherwise, all the histologic characteristics of the heredodegenerative forms of leukodystrophy, in which the disintegration predominates over the proliferative and exudative vascular process. In the glial and mesenchymal tissue one finds in our case the same functional incapacity to metabolize the derivatives of the myelin that one observes in the familial forms. Formation of these disintegrative products is retarded in the parenchyma in a metachromatic form. Five observations of unequal value, but of the same type, are found in the literature. In the case reported here there is no decisive clinical or histopathologic argument to support a separate nosologic classification. One is dealing with a disturbance, apparently of heredodegenerative type, in which the disintegration, for some unknown reason, has been observed in a metachromatic stage.

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SWEAT SECRETION IN MAN

V. DISTURBANCES OF SWEAT SECRETION WITH LESIONS OF THE PONS, MEDULLA AND CERVICAL PORTION OF CORD

CARL F. LIST, M.D.
AND
MAX M. PEET, M.D.
ANN ARBOR, MICH.

The medulla oblongata has an important influence on the secretion of sweat. This fact was first recognized in 1878 by Adamkiewicz,[1] who observed perspiration of all foot pads of the cat on electrical stimulation of the medulla. The experiments of earlier physiologists indicated that the pathways for sweating undergo a crossing at the level of the medulla oblongata and then descend in the lateral columns of the spinal cord. In 1909 Karplus and Kreidl [2] presented experimental evidence that the oculopupillary and sweating pathways descending from the hypothalamus to the upper cervical region of the cord remain uncrossed, but that each half of the cervical portion of the cord controls the sweating of all four extremities. In a recent experimental study, Magoun, Ranson and Hetherington [3] found that the descending vegetative pathways from the hypothalamus pass through the mesial and lateral portions of the pontile tegmentum as well and that the vasomotor fibers are mainly uncrossed, with a smaller crossing component before reaching the cervical region of the cord.

The clinical literature contains scattered reports describing disturbed sweat secretion in patients with lesions of the pons and medulla oblongata, but apparently these changes have not been systematically investi-

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From the Department of Surgery, the University of Michigan.

Read at the Sixty-Fourth Annual Meeting of the American Neurological Society, Atlantic City, N. J., May 3, 1938.

1. Adamkiewicz, A.: Die Secretion des Schweisses, Berlin, A. Hirschwald, 1878.

2. Karplus, J. P., and Kreidl, A.: Gehirn und Sympathicus: I. Zwischenhirnbasis und Halssympathicus, Arch. f. d. ges. Physiol. **129**:138-144 (Aug. 19) 1909. Karplus, J. P.: Die Physiologie der vegetativen Zentren, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1937, vol. 2, p. 402.

3. Magoun, H. W.; Ranson, S. W., and Hetherington, A.: Descending Connections from the Hypothalamus, Arch. Neurol. & Psychiat. **39**:1127-1149 (June) 1938.

gated.[4] From such an analysis information may be obtained as to the course of vegetative pathways in the brain stem and spinal cord. In order to study lesions of the higher vegetative connections, an adequate diaphoretic method must be used which acts centrally to the site of the lesion. The thermoregulatory sweating test [5] fulfils this requirement, since it presumably stimulates the thermoregulatory and sweating mechanism in the hypothalamus; from here the nerve impulses travel downward through the brain stem, spinal cord and thoracolumbar portion of the chain to the periphery. If, therefore, this path is affected by a lesion, abolition, or at least diminution, of sweating is to be expected.

We shall present in the following sections clinical observations on 18 patients, in 15 of whom the lesions were localized by neurologic and roentgenologic methods and in 3 of whom the lesions were produced by surgical means. The clinical diagnosis was verified by necropsy in 1 case.

PONTILE LESIONS

CASE 1.—*Tumor on the left side of the oral half of the pons. Marked generalized, symmetric hypohidrosis, except for normal sweating of the face and neck.*

F. C., a boy aged 12 years, gave a history of suboccipital headaches, dizziness, double vision, unsteady gait and occasional vomiting, of one month's duration.

Neurologic examination revealed normal fundi and definite sluggishness and limitation of the pupillary light reaction bilaterally; slight paresis of upward gaze was noted. Spontaneous conjugate deviation of both eyes to the right was present, combined with complete paralysis of voluntary conjugate horizontal gaze to the left; however, reflex movements of the eyes on turning the head passively were preserved, except for slight nucleoperipheral paresis of the left sixth nerve. Caloric stimulation of the left vestibular apparatus produced marked nystagmus to the right, with preponderance of the slow component; with stimulation on the right side only slow deviation to the right occurred. There were marked weakness, some atrophy and hyporeflexia of the left masseter muscle, associated with slight sensory disturbance in the distribution of the left fifth nerve. Slight lagophthalmos on the left side with absence of spontaneous winking was found. There was rather marked weakness (central type) of the right lower part of the face. Speech was mildly dysarthric. Right hemiparesis was present with

4. The clinical symptomatology of pontile and medullary lesions has been adequately surveyed in the comprehensive papers of Marburg (Ueber die neueren Fortschritte in der topischen Diagnostik des Pons und der Oblongata, Deutsche Ztschr. f. Nervenh. **41**:41-91, 1911) and, recently, of Környey (Symptomatologie der verlängerten Marks, der Brücke, des Mittelhirns und des Sehügels, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1937, vol. 5, p. 445).

5. Sweating is induced by application of external heat, ingestion of hot fluids and acetylsalicylic acid (List, C. F., and Peet, M. M.: Sweat Secretion in Man: Sweating Responses in Normal Persons, Arch. Neurol. & Psychiat. **39**: 1228-1237 [June] 1938).

diminution of muscle tone, but the deep reflexes were increased. There were some ataxia in the right arm and leg and dysdiadokokinesis in both hands. Spontaneous past pointing of the right hand to the right could be demonstrated. Station was unsteady, with a tendency to fall to the right and backward. Sensory examination revealed hypesthesia for superficial and deep qualities in the right upper extremity.

A diagnosis was made of a left pontile tumor extending caudally to the upper border of the facial nucleus and orally to the upper pole of the pons (fig. 1 *A*).

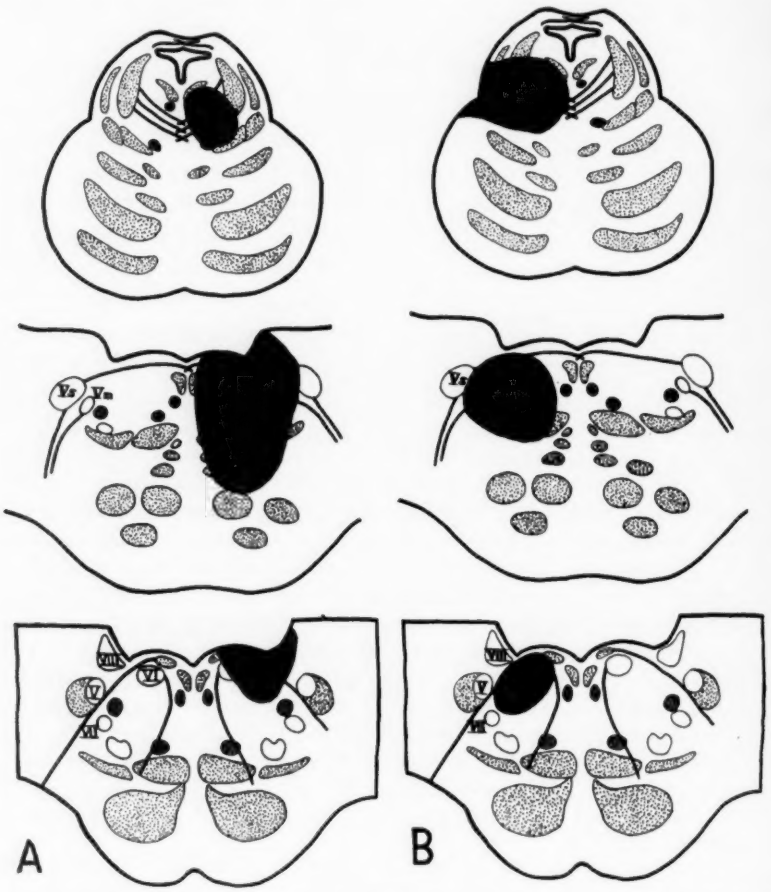

Fig. 1.—Diagrams to show the probable extent of lesions (*A*, case 1) in the upper left side of the pons and (*B*, case 4) in the tegmentum of the upper right side of the pons.

The sweating test (fig. 2 *A*) showed moderate symmetric sweating of the face and neck and marked diminution in sweating on the chest and upper extremities, which was equal on the two sides. Perspiration was slightly more pronounced on the hands. There was almost no sweating on the lower part of the trunk and the lower extremities.

CASE 2.—*Midpontile tumor, predominantly on the left side. Symmetric hypohidrosis of the trunk and extremities.*

In the case of V. G., a boy aged 10 years, three months prior to admission, the following symptoms gradually developed after a minor injury to the head:

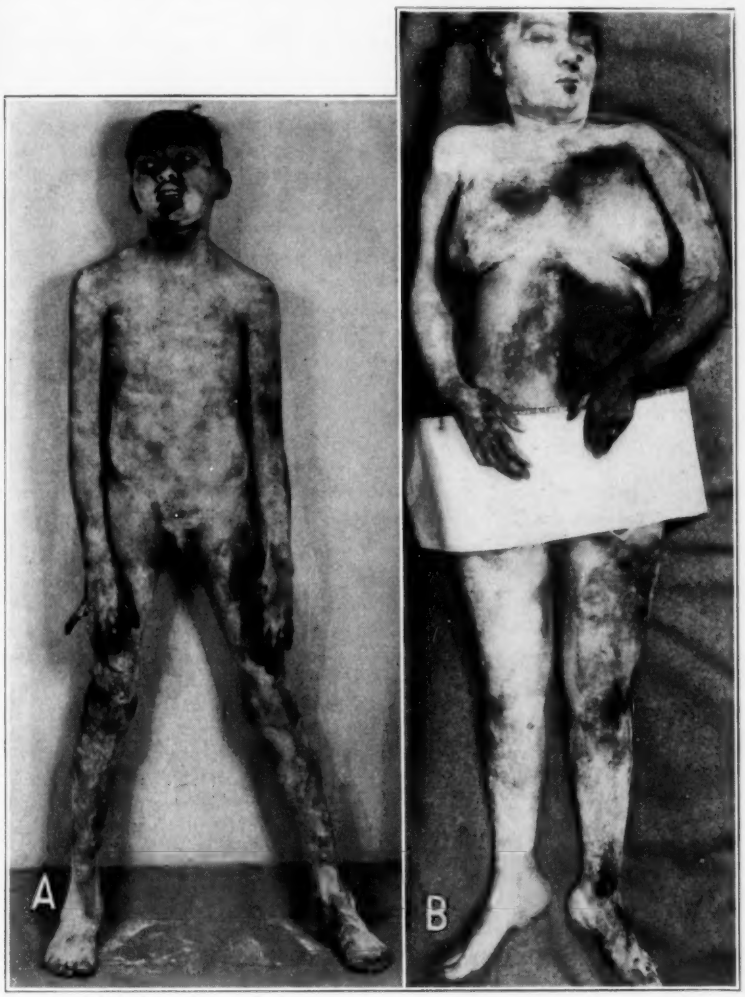

Fig. 2.—Sweating tests (*A*) in case 1, the lesion in which is illustrated in figure 1 *A*, and (*B*) in case 4, the lesion in which is shown in figure 1 *B*.

unsteadiness of gait; dizziness; diplopia; loss of hearing, chiefly on the left; inability to close the left eye completely, and some difficulty in swallowing and talking. There had been a few attacks of nausea and vomiting in association with mild suboccipital headaches.

Examination revealed slight suboccipital tenderness bilaterally, more marked on the left. The pupils and fundi were normal. A slight convergent squint of

the left eye was noted. There were paralysis of conjugate horizontal gaze, complete to the left and almost complete to the right, and slight limitation of upward and downward gaze, with some vertical nystagmus. Reflex excitability of the eye muscles, tested by producing compensatory ocular movements, was also definitely impaired in the horizontal plane, disclosing coexisting nucleoperipheral paresis of the left sixth nerve. A caloric test produced only slow deviation of both eyes to the irrigated side, but no nystagmus. There were bilateral corneal anesthesia and areflexia, and definite hypesthesia in the distribution of the left fifth nerve could be demonstrated, whereas sensory changes on the right side were doubtful. The left masseter muscle was weak. Power in the masticatory muscles on the right side was only slightly affected. Bilateral facial weakness of peripheral type was noted, more on the left than on the right, associated with increased spontaneous secretion of tears. Hearing was diminished bilaterally, particularly on the left. The palatal and gag reflexes were absent. Taste was almost completely abolished over the posterior third of the tongue on the left side and slightly diminished on the right. There were considerable dysarthria, dysphagia and drooling of saliva. There were mild tetraparesis, with weakness predominating on the right side, and mild spasticity of both legs. All tendon reflexes were markedly increased, with the Babinski sign present bilaterally and Mendel and Rossolimo signs on the right. The patient showed considerable ataxia in the arms and legs and slowing of diadokokinesis on the right. There was spontaneous past pointing of both arms to the left. Station was unsteady, and gait was asynergic and staggering. Slight sensory disturbances (thermal hypesthesia, hypalgesia and diminished vibratory sense) were noted over the entire right side of the body except the face.

A diagnosis was made of midpontile tumor, involving the left side particularly (fig. 3).

The sweating test showed normal response of the head and neck bilaterally. Symmetric, although diminished, sweating was seen over the chest and arms, and almost complete absence of perspiration was noted over the lower parts of the trunk and the lower extremities.

CASE 3.—*Old vascular lesion in the oral two thirds of the left lateral pontile tegmentum. Normal sweating response except for minimal hypohidrosis of the right half of the trunk and the right leg.*

M. M., a woman aged 48, four years prior to admission had suffered a stroke, resulting in partial paralysis and numbness of the right side of the body and blurring of speech. There had been gradual improvement of the weakness and numbness of the right side; the patient, however, had never been able to walk again, and a coarse tremor of her head and right arm developed.

Examination revealed a coarse oscillatory tremor of the head, which was usually turned to the right, and a similar oscillatory tremor of the resting right arm and hand. There was convergent strabismus of the left eye with complete paralysis of the left sixth nerve and questionable weakness of the left fourth nerve. Conjugate movements of the eyes were incoordinated, with slight limitation of horizontal gaze to the right. The muscles of mastication on the left side were weak and atrophic, but there was no sensory disturbance in the distribution of the left trigeminal nerve. The left corneal reflex was absent, but corneal sensation was intact. There was almost complete left facial palsy of peripheral type. Hearing was slightly diminished on the left. Fine myoclonic twitchings of the soft palate were seen. Speech had a cerebellar dysarthric character; it was slow, scanning and explosive. A severe cerebellar syndrome

was present bilaterally, with hypotonicity, dysdiadokokinesis and a positive rebound sign. Ataxia was severe and was most evident when the patient attempted to make intentional movements. In the right finger to nose test, particularly, an extremely coarse and violent shaking of the entire right upper extremity occurred. The patient was unable to stand or walk. Definite paresis of the extremities was not noted, but the tendon reflexes were more active on the right than on the left and the right abdominal reflexes were definitely diminished. There were no

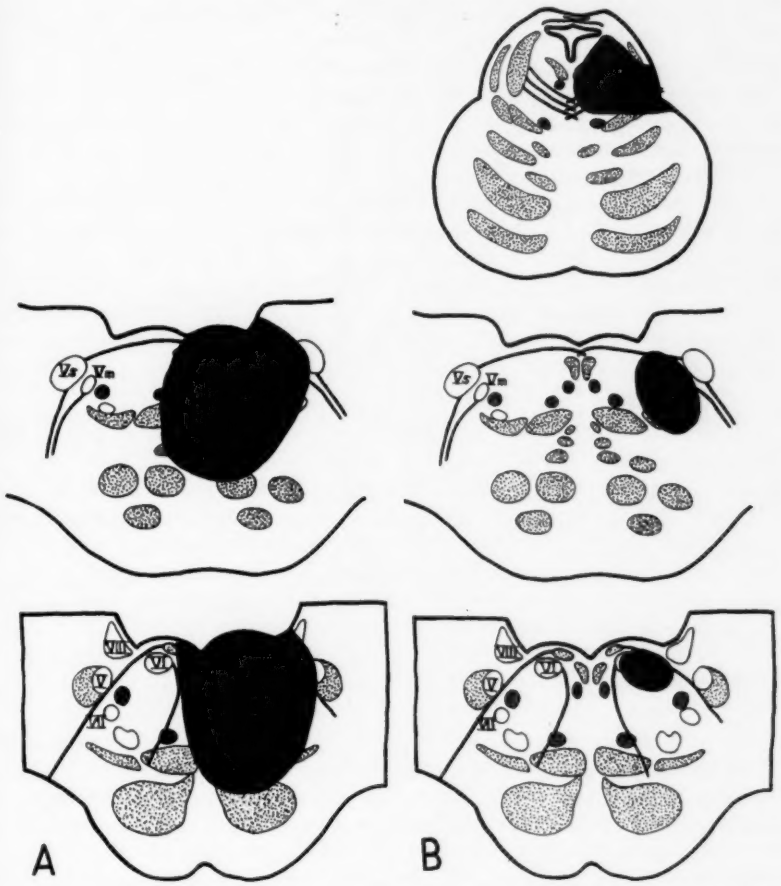

Fig. 3.—Diagrams to show the probable location of the lesions (*A*) in case 2, and (*B*) in case 3.

pathologic reflexes indicating involvement of the pyramidal tract. Sensory examination revealed hypalgesia and thermohypesthesia of the entire right side of the body, being most pronounced on the upper half of the body. There was slight diminution in vibratory sense of the right hand.

A diagnosis was made of an extensive lesion on the left side, involving the cerebellar hemisphere, the superior peduncle and the tegmentum of the upper and middle parts of the pons, which accounted for the paresis of the fourth to the

seventh nerve and the crossed sensory changes. It was thought that the lesion was probably due to softening in the distribution of the left superior cerebellar artery, possibly combined with obstruction of one of the small arteries arising from the basilar trunk (fig. 3 *B*).

The sweating test showed an almost normal response, except that the right lower half of the trunk and the right lower extremity perspired slightly less than the corresponding regions on the left side.

CASE 4.—*Fairly recent vascular lesion in the right lateral tegmental area of the oral two thirds of the pons. Right hemihypohidrosis.*

A. S., a woman aged 44, four months prior to admission suffered a stroke, after which she complained of dizziness, weakness of the left side of the body, unsteadiness and trembling of all extremities, inability to stand and to walk, double vision and disturbance of speech. The weakness of the left extremities improved somewhat, whereas all the other symptoms remained unchanged.

Examination revealed a pyknic body build, a blood pressure of 200 systolic and 120 diastolic and hypertensive heart disease. The patient's head was held rotated to the left and tipped to the left shoulder. Hypertensive neuroretinitis, with exudates, was present bilaterally. There were convergent strabismus of the right eye and severe paresis of the right sixth nerve, combined with slight weakness of conjugate gaze to the left. Horizontal-rotatory nystagmus was present bilaterally. The right corneal reflex was absent, the left diminished. Pain and tactile sensations were slightly diminished in the right trigeminal area, and the masticatory muscles on the right side were markedly paretic and atrophic. There was complete right facial palsy of peripheral type. Slight neuroparalytic keratitis was noted on the right. Hearing was moderately diminished on the left, especially for sounds of high pitch. Caloric vestibular stimulation demonstrated relative hypoexcitability on the right side as compared with the left. The right half of the soft palate showed minimal paresis and fine, rapid myoclonic twitchings. Speech was typical of cerebellar dysarthria; it was slow, scanning and explosive. The patient held her left hand in a bizarre posture, with occasional pseudoathetoid movements of the fingers; the left toes also performed occasional pseudospontaneous movements. The right hand also exhibited an unusual posture, with a tendency toward ulnar abduction and spreading of the fingers. All extremities were markedly hypotonic, especially on the right, but pareses were absent. There was coarse oscillatory tremor of the right upper extremity on intentional movement; the left upper extremity also showed gross kinetic ataxia and dysmetria. Both lower extremities were markedly ataxic. Dysdiadokokinesis was present bilaterally, more pronounced on the right. The patient was unable to stand or walk. The deep reflexes were generally hyperactive, with a brisker response in the left upper and right lower extremities. The Hoffmann sign was present bilaterally. The abdominal reflexes were not obtained, nor was the left plantar reflex, but no pathologic foot reflexes could be elicited. Sensory examination revealed profound disturbances over the entire left half of the body: Postural sense in the left upper extremity was almost completely abolished and was considerably disturbed in the left lower extremity; the sensations of pain, touch, vibration and temperature were abolished in the left upper extremity, markedly diminished in the left leg and moderately impaired over the left half of the trunk, whereas the left side of the face and neck showed minimal disturbance only.

A diagnosis was made of a vascular lesion in the right dorsolateral part of the pontile tegmentum, extending orally to the region of the isthmus and caudally to the level of the nucleus of the sixth nerve (fig. 1 *B*).

The sweating test (fig. 2 *B*) showed definite hypohydrosis on the entire right side of the body, most striking on the face, less so on the right arm and trunk and least on the right leg.

CASE 5.—*Lesion (tumor?) chiefly in the tegmentum of the lower part of the pons and upper part of the medulla on the left side. Marked left hemihypohidrosis and hemihyperthermia.*

B. S., a girl aged 7 years, was admitted with a history of diplopia, weakness of the left side of the face, drooling, unsteadiness of the right hand and staggering gait for two weeks.

Examination revealed that the fundi and pupils were normal. There was complete paralysis of horizontal gaze to the left, combined with complete paralysis of the left sixth nerve. There was moderate paresis of horizontal gaze to the right, with slight weakness of the right sixth nerve. Complete paralysis of the left seventh nerve of peripheral type was present. The left corneal reflex was absent. Considerable weakness of the masticatory muscles was noted on the left side, while sensory disturbance in the area of the left trigeminal nerve was slight. Hearing was markedly diminished on the left. The left vestibular apparatus was not excitable by caloric stimulation, and the right was almost inexcitable. Taste was diminished on the anterior two thirds of the tongue and completely abolished on the posterior third of the tongue on the left. There was marked increase in salivation. Definite paresis of the left half of the soft palate was noted, with absence of the palatal reflex on the left and diminution on the right. Sensation of the left half of the pharynx was diminished. The right arm and leg showed mild ataxia, but no paresis. The reflexes were normal except for an increase in the right ankle jerk and a positive Babinski sign on the right. The patient swayed slightly when walking, and Romberg's sign was positive.

A diagnosis was made of a pontile lesion, probably a neoplasm, involving chiefly the tegmentum on the left side. It was believed that the lesion extended orally to the middle of the pons (to the level of the masticatory nucleus) and that it reached caudally to the upper portion of the medulla oblongata (level of the nucleus of the ninth nerve) (fig. 4 *A*).

Sweating Test (fig. 5 *A*).—The patient exhibited spontaneous sweating (it was a warm summer day) only of the right side of the face. The heat sweating test revealed almost complete anhidrosis of the left side of the face and neck and marked hypohidrosis of the remainder of the left side of the body, with a sharp demarcation in the midline. Diminution of sweating was less pronounced on the lower than on the upper extremity. Sweating of the right lower extremity was perhaps also a trifle diminished. Study of cutaneous temperatures (with an outside temperature which did not induce visible spontaneous sweating) showed definite hyperthermia of the left side of the body. The left half of the face was almost 1 degree C. (0.8 degree F.) warmer than the right. The average difference in temperatures of the arms was 0.7 C. (0.6 F.), that of the legs was 0.4 C. (0.3 F.).

CASE 6.—*Recent lesion in the left lateral tegmental region of the lower part of the pons and the upper left part of the medulla oblongata. Definite hemihypohidrosis and Horner syndrome on the left side.*

D. S., a man aged 24, three weeks prior to admission became ill with violent suboccipital headaches, vomiting and dizziness. Within a few days there developed

diplopia, numbness and paralysis of the left side of the face, deafness on the left, disturbance in swallowing, severe unsteadiness, which rendered standing and walking impossible, and loss of sensation on the entire right side of the body.

Examination revealed a definite Horner syndrome on the left side. There was marked paresis of the left sixth nerve combined with mild paresis of conjugate horizontal gaze to the left and horizontal nystagmus bilaterally. Slight vertical nystagmus occurred on upward gaze. The left corneal reflex was absent, the right slightly diminished. There was complete anesthesia for the sensations of

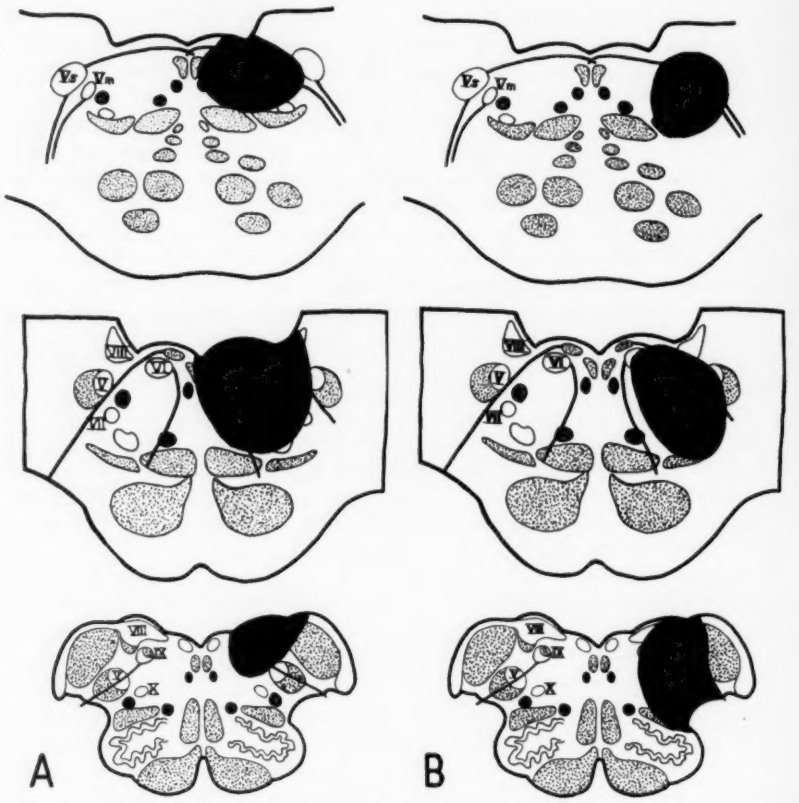

Fig. 4.—Diagrams to show the probable extent of the lesions (*A*, case 5) in the lower left side of the pons and (*B*, case 6) in the left lateral part of the lower portion of the pons and of the medulla.

touch, pain and temperature in the cutaneous and mucosal distribution of the left trigeminal nerve, and the masticatory muscles, especially the masseter, were markedly weakened on the left. Complete paralysis of the left facial nerve (of peripheral type) was present. The left ear was totally deaf, and hearing was slightly diminished on the right for sounds of high pitch. Caloric vestibular stimulation showed marked hypoexcitability on the left and a perverted and slightly diminished response on the right. Taste was abolished except on the anterior two thirds of the tongue on the right. The left half of the soft palate was slightly paretic, with abolition of palatal and gag reflexes on the left and diminution of

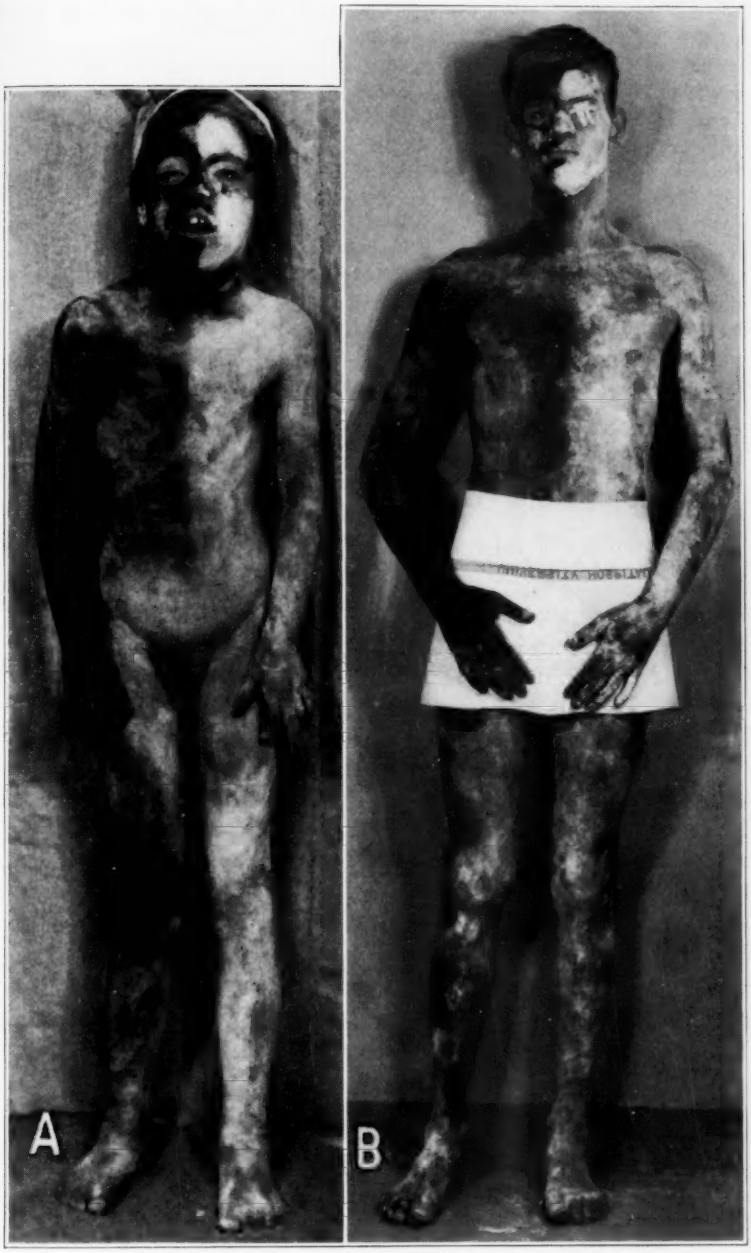

Fig. 5.—Sweating tests (*A*) in case 5, the lesion in which is shown in figure 4 *A*, and (*B*) in case 6, the lesion in which is shown in figure 4 *B*.

these reflexes on the right. The left side of the pharynx and larynx were hypesthetic, and slight paresis of the left vocal cord was found. The patient presented a mild but definite left cerebellar syndrome, with hypotonicity, slight ataxia and dysdiadokokinesis of the left extremities and a tendency to past pointing to the left. Station was asynergic, with a positive Romberg sign and a tendency to fall to the left. The gait was cerebellar, with deviation to the left. Almost complete analgesia and thermoanesthesia of the entire right side of the body were present, except in the face, where these sensations were markedly diminished only. Slight diminution of tactile sensation on the right half of the body was also demonstrable, but proprioceptive and epicritic sensations were intact. The extremities showed no motor weakness; Mayer's and Leri's reflexes were absent on the right; the abdominal reflexes were considerably diminished, and the right plantar response was absent. All other reflexes were normal.

The clinical diagnosis was a lesion in the left lateral pontile tegmentum and dorsolateral part of the medulla oblongata, reaching orally to the level of the main sensory trigeminal nucleus and caudally to the upper part of the nucleus ambiguus (fig. 4*B*).

The sweating test (fig. 5*B*) showed considerable hemihypohidrosis on the left side, which was most noticeable on the face and upper extremity.

Summary.—Sweating responses in 6 cases of pontile lesion showed considerable variation. In 2 instances of tumor with unilateral (case 1) or predominantly unilateral (case 2) invasion of both the tegmental and the peduncular portion of the upper and middle parts of the pons, sweating showed bilaterally symmetric diminution except for the face and neck. There was almost complete anhidrosis of both lower extremities. In 2 almost identical cases of vascular lesion in the lateral tegmentum of the upper two thirds of the pons the sweating responses differed greatly. In 1 instance, that of an old lesion (case 3), sweating was practically normal except for minimal diminution on the leg and side of the trunk contralateral to the lesion. In the other case, one of a rather recent lesion (case 4), there was definite ipsilateral hemihypohidrosis. In 2 further observations (cases 5 and 6), the lesions were situated in the dorsolateral tegmentum and involved the lower portion of the pons and the upper part of the medulla oblongata. In both cases striking ipsilateral hemihypohidrosis was present, which was most pronounced on the face and neck and least on the lower extremity. In 1 of these cases a Horner syndrome was present.

LESIONS OF THE MEDULLA OBLONGATA

CASE 7.—*Vascular lesion situated in the left lateral region of the medulla oblongata. Hemihypohidrosis involving chiefly the left side of the face and neck and left upper extremity. Horner's syndrome on the left.*

C. E., a man aged 51, gave a history of attacks of dizziness during the preceding year. Ten months prior to admission, after an attack of dizziness, there suddenly developed marked weakness of the right arm and leg. He also noticed that he did not perspire on the left half of the face.

Examination showed a plethoric man, with a blood pressure of 140 systolic and 86 diastolic and mild diabetes. Neurologic examination disclosed a Horner syndrome on the left side. There were coarse horizontal-rotatory nystagmus to the left and fine nystagmus to the right. The left corneal reflex was almost absent. Marked hypalgesia, thermohypesthesia and slight tactile hypesthesia were found in the distribution of the left fifth nerve. These sensory changes were most pronounced in the first and second divisions, whereas they were slight in the cutaneous distribution of the third division and entirely absent on the tongue. Slight weakness of the left side of the soft palate was present; the motility of the larynx was normal, however. Speech had a bulbar dysarthric character. A mild cerebellar syndrome was present on the left, whereas moderate spastic hemiparesis was noted on the right, more pronounced in the leg than in the arm. Tendon reflexes were increased on the right, with pathologic toe signs. Sensory examination demonstrated definite hypalgesia and thermohypesthesia on the right side, extending downward from the ear-chin line; below the sixth dorsal segment temperature sensation was completely abolished. The gait was broad based, with a slight paretic quality in the right leg and a tendency to deviate to the left. Romberg's sign was positive, with a tendency to fall to the left.

A diagnosis of a lesion in the left lateral part of the medulla oblongata was made. The presence of spastic hemiparesis and absence of involvement of the vocal cords were considered as evidence of a rather high, partial occlusion of the left vertebral artery (fig. 6*A*).[6]

The sweating test showed (fig. 6*C*) definite left hemihypohidrosis. Perspiration was almost completely absent on the left side of the face and neck. It was markedly diminished on the upper part of the chest and of the left upper extremity. There was only slight diminution of sweating on the lower extremity and no definite change on the abdomen. Studies of cutaneous temperature showed slightly higher temperatures on the entire left side of the body than on the right.

CASE 8.—*Recent vascular lesion in the right dorsolateral area of the medulla oblongata. Horner's syndrome on the right side. Right hemihypohidrosis, especially of the face, neck and arm.*

W. L., a man aged 45, ten days prior to admission awoke with marked dizziness, nausea, sweating and coldness of the left side of the body. Since that time he had also noticed staggering to the right and hoarseness.

Examination revealed a Horner syndrome on the right side. The corneal reflex was almost absent on the right and diminished on the left. Slight weakness of the lower portion of the right facial nerve was noted. Sensation of taste was undisturbed. The soft palate showed no paresis, and the palatal and gag reflexes were normal. No sensory changes could be demonstrated in the pharynx. Laryngoscopic examination disclosed palsy of the right vocal cord. There were slight cerebellar signs on the right side, consisting of hypotonicity in the right arm, with rebound phenomenon, spontaneous past pointing to the right, poor performance of the finger to nose test on that side and dysdiadokokinesis. The tendon reflexes were normal, but the abdominal reflexes were weaker on the left than on the right. The sensations of pain and temperature were profoundly disturbed over the entire left side of the body except for the trigeminal area. Sensation for

6. The clinical symptoms in this case corresponded with the "upper lateral hemibulbar syndrome" of Foix, Hillemand and Schalit, which these authors explained by an occlusion of the "lateral artery of the bulb," a direct branch from the basilar artery.

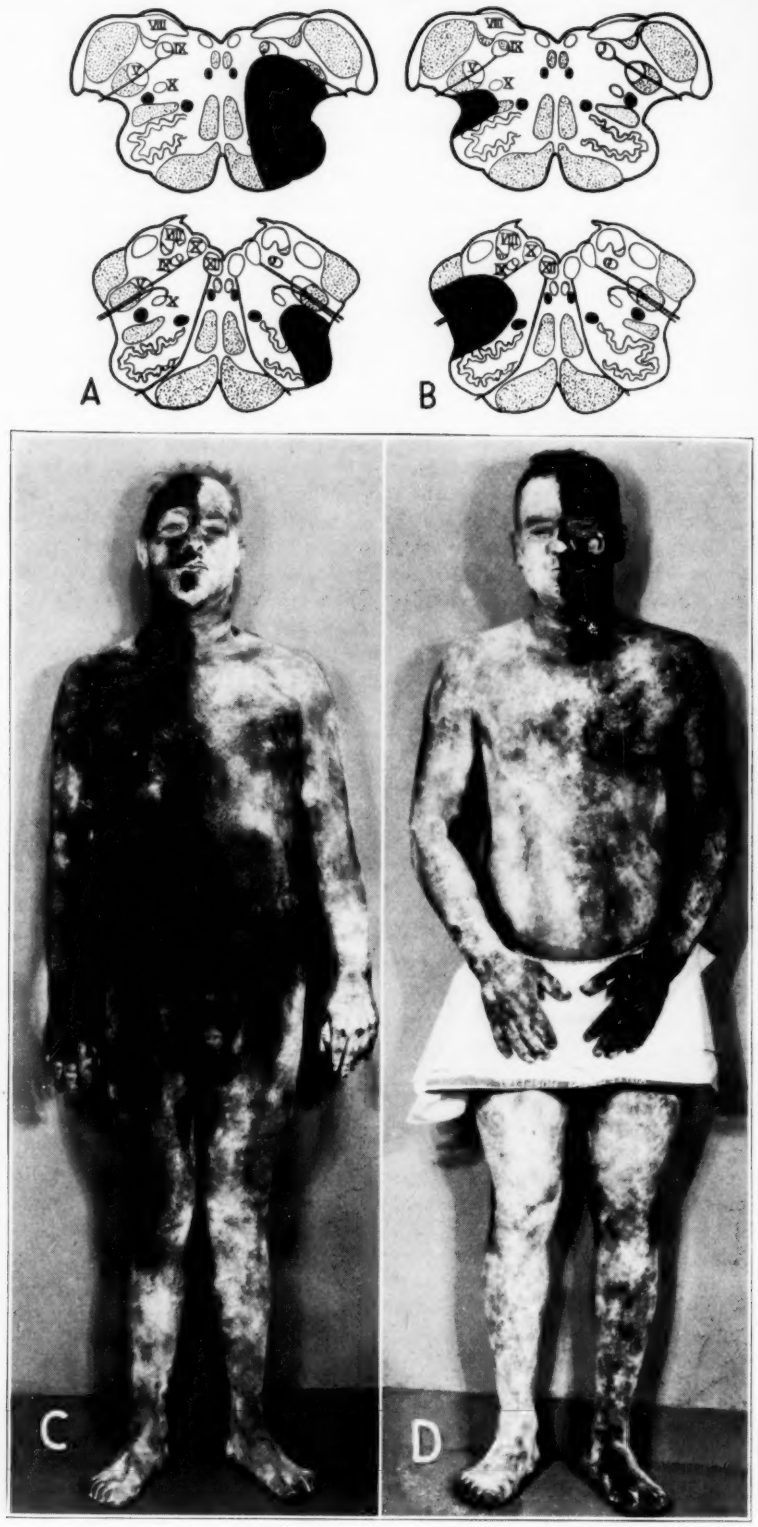

Fig. 6.—*A* (case 7), diagram to show probable extent of the lesion in the left lateral portion of the medulla oblongata; *B* (case 8), diagram to show the lesion in the right lateral part of the medulla oblongata; *C*, sweating test in case 7, the lesion in which is shown in *A*, and *D*, sweating test in case 8, the lesion in which is shown in *B*.

warmth was not felt at all. Sensation for cold was replaced by a distorted feeling of pain of a peculiar hyperpathic character. Sensation of pain was not appreciated as such, but was experienced as a peculiar dysesthesia. Tactile sensation showed also minimal diminution over the left side of the body, but the other sensory qualities were not interfered with.

A diagnosis of a syndrome referable to the right lower dorsolateral part of the medulla oblongata was made, presumably due to a vascular lesion in the distribution of the posterior inferior cerebellar artery (fig. 6*B*).

Sweating Response (fig. 6*D*).—The patient exhibited spontaneous hyperhidrosis of the left side of the face and neck and the left arm. These parts felt much colder than the corresponding parts on the right. A heat sweating test revealed marked diminution of sweating over the entire right side of the body and relative hyperhidrosis of the left side, particularly the face. The difference in sweating on the two sides was most marked on the face and neck, less on the arms, still less on the legs and least marked on the trunk.

CASE 9.—*Old vascular lesion in the left dorsolateral area of the medulla oblongata. Ipsilateral hypohidrosis of the upper half of the body. Horner's syndrome on the left side.*

J. T., a man aged 66, four months previous to admission had a sudden attack, after which he experienced dizziness, staggering, weakness of the left side of the body, severe disturbance of speech and of swallowing and numbness of the left side of the face and the right side of the body. Except for the dizziness and unsteadiness of gait, all symptoms had gradually improved.

Examination revealed marked myocardial changes, auricular fibrillation and a blood pressure of 160 systolic and 90 diastolic. The patient held his head tipped slightly toward the right shoulder. There was a Horner syndrome on the left side. Questionable bilateral weakness of the sixth nerve, combined with bilateral horizontal nystagmus, was observed. The left corneal reflex was abolished; the right was intact. Definite hypesthesia for touch, pain and temperature sensations was found in the distribution of the first division of the left fifth nerve, whereas in the area of the second division only slight hypesthesia was present and sensation was normal over the distribution of the third division. Incomplete nerve deafness was present bilaterally, more pronounced on the left. The soft palate showed minimal weakness on the left side, and the palatal and gag reflexes were absent on that side. Taste was markedly diminished on the entire left side of the tongue, and hypesthesia was found on the left side of the pharynx. The left vocal cord was completely paralyzed. There was a definite, although not severe, cerebellar syndrome on the left, consisting of slight ataxia in performing the finger to nose test on that side, spontaneous past pointing with the left arm to the left and a broad-based, staggering gait with deviation and a tendency to fall to the left. On the right side severe loss of pain and temperature sensation was noted, except over the trigeminal area. There were also slight diminution of tactile sensation over the right half of the body and mild impairment of vibratory sense in the right leg. The sensory disturbances were more profound in the right lower than in the right upper extremity. There were no reflex changes except for diminution of the abdominal reflexes and an equivocal plantar response on the right.

A diagnosis was made of a residual lesion in the left dorsolateral portion of the medulla oblongata, probably due to thrombosis of the posterior inferior cerebellar artery.

The sweating test showed marked diminution of sweating on the left side of the head and neck and, to a lesser degree, on the upper left side of the chest and the left upper extremity.

CASE 10.—*Small vascular lesion in the left lateral portion of the medulla oblongata. Left hemihypohidrosis of the face and neck. Horner's syndrome on the left side.*

L. R., a man aged 34, five months previously, after marked physical effort, had had an attack of dizziness, following which he noticed loss of temperature sensation on the right half of his body.

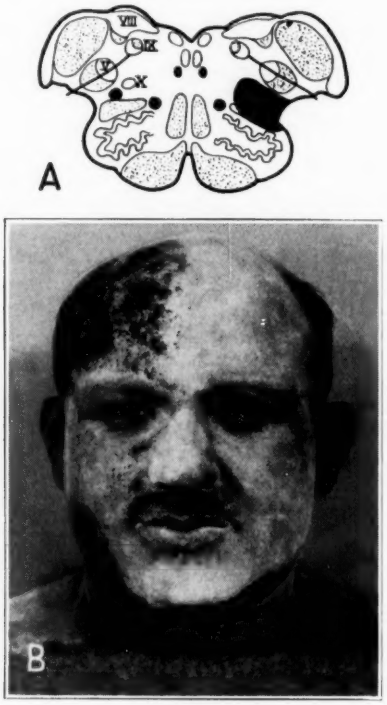

Fig. 7 (case 10).—Small lesion in the left lateral portion of the medulla oblongata. *A*, diagram to show the probable site of the lesion, and *B*, sweating test.

Examination showed an obese man, with a blood pressure of 200 systolic and 130 diastolic. A definite Horner syndrome was present on the left side. The corneal reflexes were normal and equal. Marked paresis of the left half of the soft palate and some hypesthesia of the left side of the pharynx were noted, but motility of the vocal cords was normal. Definite thermohypesthesia and hypalgesia were present on the right half of the body except in the distribution of the first division of the trigeminal nerve. The sensory disturbances were most severe on the leg and gradually diminished upward.

A diagnosis of a small vascular lesion (of hypertensive origin) situated in the left lateral area of the medulla oblongata (fig. 7 *A*) was made.

The sweating test (fig. 7 *B*) disclosed definite hypohidrosis on the left side of the head and neck and relative hyperhidrosis on the right side. Minimal diminution of sweating was also noted on the left leg.

Although in the following observation the location and extent of the anatomic lesion were almost identical with those in cases 8 and 9, the sweating response was entirely different.

CASE 11.—*Acute vascular lesion in the left dorsolateral area of the medulla oblongata. "Hemihypohidrosis cruciata" of the right arm and right half of the trunk and of the left leg. Horner's syndrome on the left.*

A. S., a man aged 47, for a year had suffered from attacks of dizziness associated with nausea, vomiting and tinnitus. He was admitted to the hospital because after his last attack of dizziness, which had occurred two days previously, difficulties in talking and swallowing and unsteadiness of the left side of the body developed.

Examination disclosed signs of general arteriosclerosis and arterial hypertension (blood pressure 200 systolic and 120 diastolic). There was a definite Horner syndrome on the left. Slight spontaneous conjugate deviation of the eyes to the left was present, associated with spontaneous nystagmus to the right. On looking to the left coarse horizontal nystagmus appeared; on looking to the right the nystagmus became less intense. There was also slight vertical nystagmus on looking upward. The corneal reflexes were absent bilaterally. All modes of sensation in the area of the left fifth nerve were markedly diminished, especially those of pain and temperature. There was slight weakness of the muscles of the lower left side of the face. Mild nerve deafness was found bilaterally, more marked on the left. The left half of the soft palate, pharynx and larynx was paralyzed, with resulting severe dysarthria and dysphagia. A pronounced cerebellar syndrome was present on the left, involving the arm more than the leg. On the right side of the body the sensations of pain and temperature were markedly diminished below the "ear-chin line." The tendon reflexes were more active on the right, and a Babinski sign was elicited on that side.

The clinical syndrome was typical of recent thrombosis of the left posterior inferior cerebellar artery or of partial occlusion of the left vertebral artery.

Necropsy.[7]—Macroscopic Observations: There was marked arteriosclerosis of the basilar and vertebral arteries and their branches. An extensive cortical softening was present in the inferior portion of the right cerebellar hemisphere, involving the lobus biventer. Another softening on the left side destroyed the cortex of the inferior vermis, the cerebellar roof nuclei and the mesial portion of the left dentate nucleus. A third softening occupied the left lateral and dorsolateral part of the medulla oblongata, which appeared to be slightly atrophic in general.

Microscopic Study of the Medullary Lesion (serial sections stained after the method of Weigert and Pal): [8] The lesion on the left side began at the cranial end of the medulla and extended caudally to the first cervical segment of the cord. The lower part of the lesion possibly was an independent softening which had coalesced secondarily with the main medullary lesion. In the most cranial sections the lesion began in the left corpus restiforme; it then enlarged, involving the lateral and medial vestibular nuclei, the descending vestibular root, the nucleus and

7. The specimen was obtained from Dr. R. U. Light, Kalamazoo, Mich.

8. The sections were prepared by Dr. K. Löwenberg, neuropathologist at the Neuropsychiatric Institute, University of Michigan.

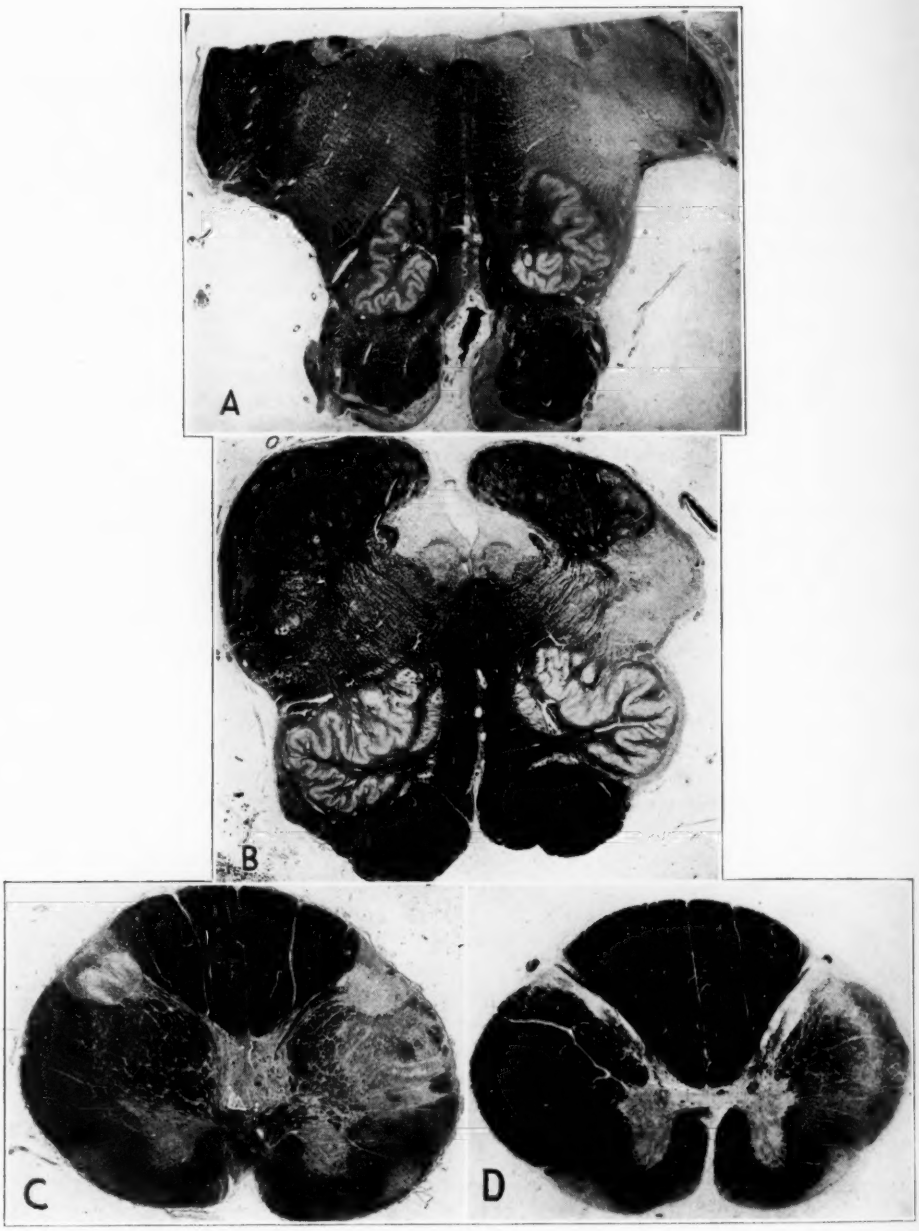

Fig. 8 (case 11).—Lesion of the left lateral portion of the medulla oblongata shown in sections of the medulla oblongata and cervical region of the cord (Weigert-Pal stain for myelin).

A, medulla oblongata at the midolivary level. The floor of the fourth ventricle is incomplete, since this section forms the end of a block which was cut obliquely. *B*, medulla oblongata at the caudal end of the fourth ventricle. *C*, spinomedullary junction (level of the pyramidal decussation). *D*, the spinal cord between the second and the third cervical segment.

tract of the descending root of the fifth nerve and slightly also the dorsal cochlear nucleus. The softening attained its largest size at the midolivary level (figs. 8 *A* and *B*). Here it destroyed the greater part of the restiform body, the descending vestibular root, the entire nucleus and tract of the descending root of the fifth nerve, the nucleus of the tractus solitarius and partially the tract itself, the crossing root fibers of the ninth and tenth nerves and almost the entire lateral reticular substance, with the nucleus ambiguus and the reticularis lateralis and various fiber tracts passing through this region, viz.: the ventral spinocerebellar, thalamo-olivary, lateral reticulospinal and lateral tectospinal, rubrospinal and lateral

Fig. 9 (case 11).—Sweating test.

spinothalamic tracts and, to some extent, the olivocerebellar and superficial external arcuate fibers. Both inferior olives showed secondary changes, which were in part due to the cerebellar lesions. At the level of the crossing of the medial lemnisci the lesion was smaller and destroyed the nucleus and tract of the descending root of the fifth nerve, a large part of the cuneate nucleus and the lateral reticular substance, with the previously mentioned descending and ascending pathways. At the level of the pyramidal decussation (fig. 8 *C*) the lesion involved the nucleus and tract of the descending root of the fifth nerve, the lateral portion of the already crossed lateral corticospinal tract and adjacent tracts in the lateral

funiculus. Slight diffuse demyelination of the right corticospinal tract, apparently retrograde in nature, was noted also above the level of the pyramidal decussation (in the medulla oblongata). At the border of the second or third cervical segment (fig. 8 *D*) there was moderate diffuse demyelination in the left anterolateral and lateral funiculus, with heavy, crescent-shaped demyelination of the lateral portion of the lateral corticospinal path and adjacent tracts in the lateral funiculus (rubrospinal and lateral reticulospinal tracts).

The sweating test (fig. 9) gave an unexpected result. Only at the beginning of the test was minimal hypohidrosis present on the left side of the face; it was not noticeable in the later stages of the procedure. Marked diminution of sweating was seen on the right upper extremity, the right upper half of the trunk and the left lower extremity. There may have been slight reduction of perspiration on the right leg as well. Measurement of cutaneous temperatures revealed slight hyperthermia of the left side of the head and neck and the left lower extremity.

Summary.—Cases 7 to 11 are instances of unilateral vascular lesions situated in the dorsolateral "retro-olivary" area of the medulla oblongata. In all instances an ipsilateral Horner syndrome was noted, and more or less marked ipsilateral hemihypohidrosis was present in cases 7 to 10. Diminution of sweating was consistently most pronounced in the area of the head, neck and shoulder, less evident on the upper extremity and least on the trunk and lower extremity. Even so small a lesion as that in case 10 modified the sweating of the head and neck considerably. The sweating response on the side opposite the lesion often tended to be overactive. In an otherwise typical case of a recent lateral lesion of the medulla oblongata (case 11) there was "hemihypohidrosis cruciata," viz., diminished sweating of the upper extremity and upper half of the trunk on the opposite side and marked hypohidrosis of the lower half of the trunk and leg on the same side. While there was only minimal hypohidrosis on the same side of the head and neck, a definite ipsilateral Horner syndrome and ipsilateral paresis of the vasoconstrictor fibers of the head, neck and leg were demonstrated.

LESIONS OF THE CERVICAL REGION OF THE CORD

CASE 12.—*Complete acute transverse syndrome of traumatic origin, with lesion at the fifth cervical segment. Anhidrosis of the entire body and loss of thermoregulation.*

A. G., a man aged 42, one day before admission struck his head when diving into shallow water. Both arms and legs were immediately paralyzed.

Examination revealed a fracture of the fifth cervical vertebra with dislocation on the sixth. Complete motor and sensory paralysis was present below the fifth cervical segment. Bilateral pupillary miosis was noted, but no sympathetic ptosis. The patient had been brought to the hospital on an extremely warm, humid day and had been covered by heavy woolen blankets in the ambulance car. On arrival his rectal temperature was 107.6 F. The skin of the entire body was flushed, but completely dry. Subsequently, his temperature dropped to 102 F., but despite the intense summer heat he never showed the slightest trace of perspiration. The patient died four days after admission, of respiratory paralysis. Permission for autopsy was not obtained.

CASE 13.—*Almost a complete acute transverse syndrome of traumatic origin, with lesion at the sixth cervical segment. Bilateral Horner's syndrome. General anhidrosis and loss of thermoregulation.*

M. H., a woman aged 21, two days prior to admission broke her neck by diving into shallow water. Immediate paralysis of the legs and partial paralysis of the arms resulted.

Examination revealed a Horner syndrome bilaterally. There was complete flaccid paralysis of the muscles of the trunk and lower extremities. The muscles of the shoulder girdle, and the biceps and brachioradialis muscles showed practically normal function, whereas all other muscles of the upper extremities were paralyzed. All tendon reflexes were abolished. There were diminution of sensation below the sixth cervical dermatome bilaterally and complete anesthesia below the eighth cervical segment. Roentgen examination revealed fracture of the fifth cervical body with dislocation on the sixth cervical vertebra.

The diagnosis was made of fracture-dislocation of the fifth on the sixth cervical vertebra, with consecutive, almost complete transverse myelitis at the lower border of the sixth cervical segment.

The heat sweating test revealed complete anhidrosis of the entire body. It may be noted that a second sweating test with mecholyl produced moderate perspiration of the entire body. During the course of her illness in the hospital the patient had an irregular temperature of 101 to 103 F., which was not accounted for by any infection.

CASE 14.—*Acute traumatic Brown-Séquard syndrome on the left side with lesion at the fourth cervical segment. Horner's syndrome on the left. Left hemihypohidrosis, especially of the face and neck.*

O. C., a boy aged 10, ten days prior to admission was wounded by a shotgun charge entering the left lateral region of the neck, immediately below and behind the lower ramus of the mandible. Shortly afterward paralysis of the left arm and leg developed.

Examination showed a Horner syndrome on the left. There was severe hemiparesis of the left arm and leg, which was still in the flaccid stage. Sensations of pain and temperature were diminished on the right side of the body below the fourth cervical segment; complete analgesia and thermoanesthesia were found below the third dorsal segment. Position sense of the fingers and toes on the left side was gravely disturbed, and vibratory sense and the ability to recognize numbers written on the skin were considerably diminished on the left side below the fourth cervical segment. Roentgen examination showed one pellet inside the spinal canal at the level of the fourth cervical body.

The diagnosis was a traumatic Brown-Séquard syndrome on the left side with a lesion at the level of the fourth cervical segment. One could not be sure whether or not the Horner syndrome was due to an additional injury to the left superior cervical sympathetic ganglion, although this seemed unlikely.

The sweating test showed definite hypohidrosis of the left side of the face and slight hypohidrosis of the left arm and leg.

CASE 15.—*Acute traumatic Brown-Séquard syndrome on the left side with lesion at the sixth cervical segment. Horner syndrome on the left side. Marked left hemihypohidrosis.*

E. A., a man aged 57, four days previous to admission sustained an injury of the neck, with immediate paralysis of the left side of the body and slight weakness of the right side.

Examination revealed a fracture-dislocation of the fifth on the sixth cervical vertebra. There was a Horner syndrome on the left side. The semiflexed left upper extremity was hypotonic. The left deltoid, biceps and brachioradialis muscles were slightly paretic; the triceps, extensor carpi radialis and flexor carpi radialis muscles showed severe paresis. All other muscles of the left forearm and hand were completely paralyzed. The left biceps and radial reflexes were diminished, but the pronator and triceps reflexes were exaggerated on both sides and there was a positive Hoffmann sign bilaterally. Mayer's reflex was absent on the left but normal on the right. The left intercostal and abdominal muscles were paretic, and the left

Fig. 10 (case 15).—Brown-Séquard syndrome on the left side with lesion at the sixth cervical segment. *A*, diagram of the lesion; *B*, sweating test.

lower extremity showed considerable predilection paresis. The abdominal reflexes were absent bilaterally. The knee and ankle reflexes were exaggerated on both sides, especially on the left, and there was a Babinski sign on the left. Sensory examination revealed hypalgesia and mild thermal hypesthesia in from the sixth cervical to the second dorsal dermatomes on the left side. On the right side the sensations of pain and temperature were considerably diminished below the sixth cervical segment and were completely abolished below the middorsal segments. Deep sensation was intact bilaterally.

A diagnosis of a post-traumatic Brown-Séquard syndrome on the left side with a lesion at the level of the sixth cervical segment was made (fig. 10 *A*).

A sweating test (fig. 10 *B*) showed severe hypohidrosis, almost anhidrosis, of the entire left half of the body. There was also moderate hypohidrosis of the right leg.

CASE 16.—*Left anterolateral chordotomy at the third cervical segment. Horner's syndrome and hemihypohidrosis on the left side.*

In the case of G.,[9] a man, a left chordotomy was performed at the level of the third cervical segment to relieve severe causalgic pain of the right hand. Complete analgesia and thermoanesthesia on the right side of the body below the third cervical dermatome resulted. On the left there was a positive Babinski sign. There was a Horner syndrome on the left.

The sweating test (made three weeks after the operation) revealed definite hypohidrosis of the entire left half of the body, being most pronounced on the face and neck (fig. 11 *B*).

CASE 17.—*Left anterolateral chordotomy below the second cervical segment. Horner's syndrome on the left. Hemihypohidrosis of the left side of the face and neck.*

T. H., a man aged 45, seventeen years before had suffered a fracture of the right clavicle and scapula, with injury to the right brachial plexus. Although the objective signs of the lesion of the plexus had disappeared, intractable severe pains in the right arm persisted.

Neurologic examination revealed no abnormal objective findings. A left chordotomy was performed at the lower border of the second cervical segment, and, in addition, the right third posterior cervical root was severed. The operation produced complete analgesia and thermoanesthesia below the second cervical segment on the right, with disappearance of the spontaneous pain. There was a definite Horner syndrome on the left. After the operation the patient had slight paresis of the left arm and disturbances of bladder function, which disappeared within a few days.

A sweating test, performed three weeks postoperatively, revealed marked hypohidrosis of the left side of the head and neck. While the upper extremities showed no difference in sweating, the left side of the trunk perspired a trifle more than the right. Postoperative measurements of skin temperatures showed slight hyperthermia of the left half of the body (the side of the lesion), except for the leg. The greatest difference was found in the temperatures of the two hands (1.3 C., or 2.3 F., warmer on the left).

CASE 18.—*Left anterolateral chordotomy at the second cervical segment. Horner's syndrome. Hypohidrosis of the face and neck.*

G. S., a man aged 53, two years prior to admission had had the right arm amputated at the shoulder joint, after a crushing injury. The patient complained of an exceedingly painful "phantom arm" and of unbearable tenderness of the amputation stump. High cervical chordotomy was performed on the left side at the level of the second cervical segment. After the operation the phantom sensation and pain in the stump disappeared. There were complete analgesia and thermoanesthesia of the entire right half of the body below the lower border

9. This case was previously reported by Guttmann and List. The patient was not registered in the hospital.

of the second cervical segment. A Horner syndrome was also found on the left. Postoperatively there was slight left hemiparesis, which disappeared within a few days.

A sweating test (fig. 11 *B*), performed two weeks after operation, showed pronounced hypohidrosis of the left half of the face and neck.

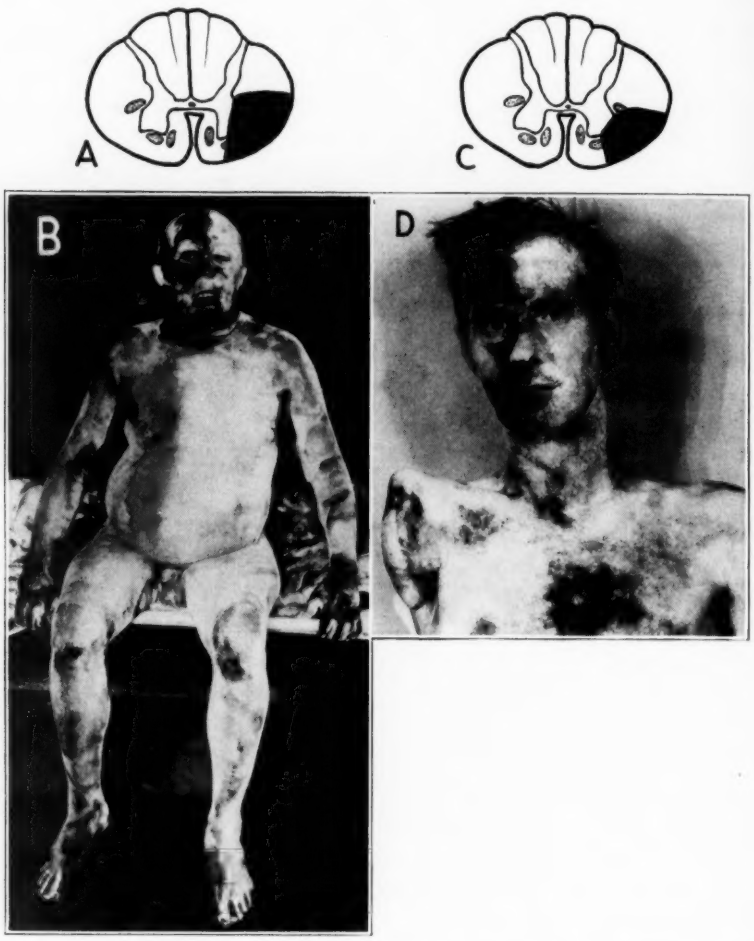

Fig. 11.—Left anterolateral chordotomies at the cranial end of the third cervical segment. *A*, diagram of the lesion in case 16; *B*, sweating test in case 16; *C*, diagram of the lesion in case 18, and *D*, sweating test in case 18.

Summary.—In 2 cases of a recent transverse syndrome at the level of the fifth (case 12) and the sixth (case 13) cervical segment, complete thermoregulatory anhidrosis, paralysis of vasoconstrictor fibers and a bilateral Horner syndrome were shown.

In 2 cases of the Brown-Séquard syndrome at the fourth and the sixth cervical segment, respectively, and in 3 cases of chordotomy at the level of the second or third cervical segment the sweating responses were similar to those observed in cases of unilateral lesions of the medulla oblongata. There was either incomplete ipsilateral hemihypohidrosis or regional hypohidrosis of the ipsilateral half of the head and neck, combined with an ipsilateral Horner syndrome and paresis of vasoconstrictor fibers. The disturbance of sweating was slightly more pronounced in cases of the Brown-Séquard syndrome than in those of chordotomy.

COMMENT

Having described the sweating responses associated with various lesions, we shall now attempt to outline the probable course of the central vegetative pathways which may also mediate impulses for thermoregulatory perspiration. That the extent of the lesion was anatomically verified in only 1 observation must make one especially cautious in drawing conclusions; yet we believe that the following deductions are based on sufficiently reliable clinical evidence.

As to the anatomic side of the problem: One must admit that present knowledge of vegetative pathways in the brain stem and the cervical region of the cord is still incomplete and contains many controversial points. Most anatomic data have been obtained from animal experimentation, but, unfortunately, the problem of thermoregulatory sweating is extremely difficult to approach from the experimental side, since sweating responses of usual laboratory animals are entirely different from those of man. In the description of the probable central vegetative pathways we shall follow an outline given by Crosby and her associates[10] (fig. 12). We do not claim that the pathways to be enumerated are the only existing central vegetative tracts, nor do we believe that the fibers of these paths are exclusively vegetative in function. Scattered throughout the brain stem are probably numerous other vegetative fiber tracts which hitherto have defied accurate topographic analysis.

The hypothalamus is linked to vegetative nuclei of the intermediolateral columns of the cord by a system of fiber tracts, which may be divided in two parts. A. An "upper neuron system" links the hypothalamus with the tegmental nuclei of the midbrain and with the reticular nuclei of the pons and medulla oblongata (fig. 12). (1) The hypothalmotegmental bundle, a presumably uncrossed tract,

10. Ariëns Kappers, C. U.; Huber, G. C., and Crosby, E. C.: The Comparative Anatomy of the Nervous System of Vertebrates, Including Man, New York, The Macmillan Company, 1936, vol. 1, pp. 269 and 657-662.

Dr. E. Crosby has assisted us in the presentation of the anatomic data, which are in part the result of her own research done in the department of anatomy of the University of Michigan.

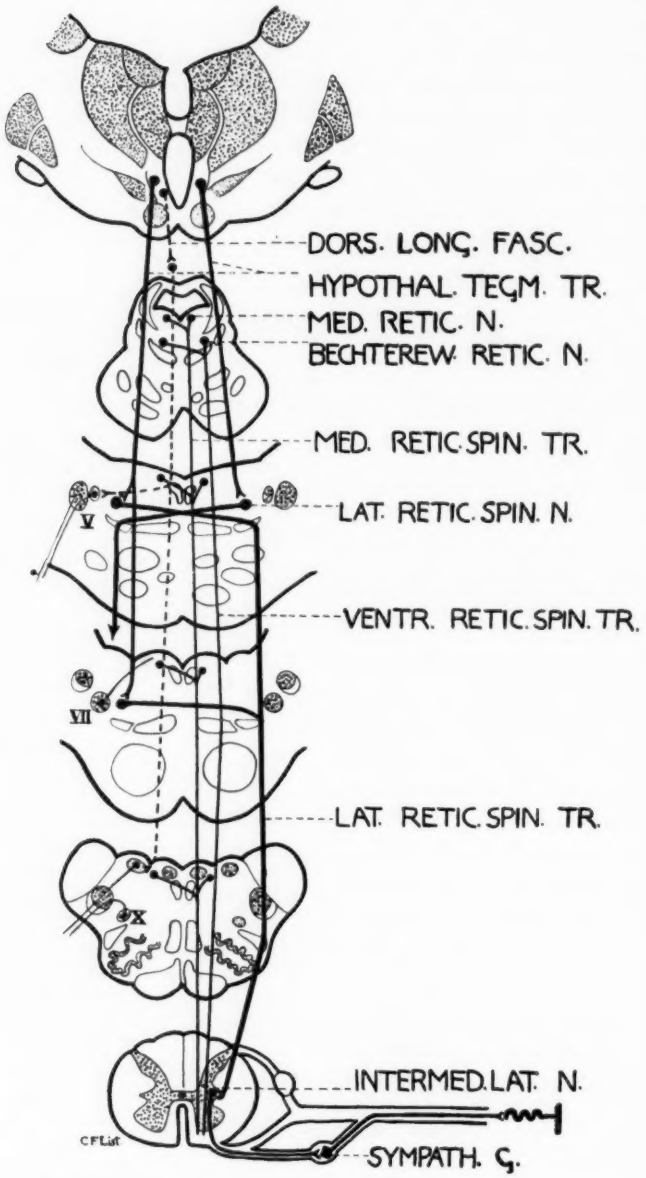

Fig. 12.—Diagram to show the probable pathways of thermoregulatory sweating (hypothalamotegmental and reticulospinal connections).

passes to the lateral reticular gray matter of the pons and medulla oblongata, with or without undergoing synapses in the substantia nigra and in the tectum. (2) The dorsal longitudinal bundle of Schütz descends from the hypothalamus to the ipsilateral dorsal tegmental nucleus and to nuclei of various cranial nerves.

B. A "lower neuron system" connecting the gray matter of the brain stem with the spinal cord includes the following fiber tracts (Papez;[11] fig. 12): (1) The medial reticulospinal tract originates in cells of the dorsal tegmental nucleus, which extends the entire length of the pons; it contains crossed and uncrossed fibers. Passing through the dorsomedial portion of the tegmentum, near the ventral and lateral aspect of the medial longitudinal fascicle, the medial reticulospinal bundle descends to the anterior tract of the cord, where it synapses with cells of the ipsilateral anterior and intermediolateral columns. (2) The ventral reticulospinal tract arises from the ipsilateral and contralateral reticular nuclei of Bechterew, which are situated in the oral portion of the pontile tegmentum dorsal to the area of the medial lemniscus. In the pons the descending bundle occupies a position slightly dorsal to the medial lemniscus; in the medulla it lies dorsal to the dorsal accessory olivary nucleus, and in the spinal cord it passes through the anterior tract close to the gray matter. (3) The lateral reticulospinal bundle probably is a crossed pathway, arising in the lateral reticular gray matter. Its nucleus of origin lies at the midpontile level, medial and ventral to the motor trigeminal nucleus. After decussation, the lateral reticulospinal fibers pass through an area dorsal to the facial nucleus and medial to the nucleus of the descending root of the fifth nerve. In the medulla oblongata the position of this bundle is slightly dorsal to the area of the lateral spinothalamic tract, lateral to the nucleus ambiguus and ventral to the nucleus of the descending root of the fifth nerve. In the spinal cord it passes through the innermost layers of the anterolateral tract in order to synapse with cells of the intermediolateral column and of the intermediate zone.

With regard to the clinical observations, one must admit that it is difficult to make definite statements as to the site and course of sweat fibers in the pons. Not only are cases of pontile neoplasm less suited to anatomic analysis than those of the more sharply demarcated vascular lesions, but in 2 cases (nos. 3 and 4) of anatomically identical vascular lesions the sweating responses were entirely different. The reason for such surprising incongruence may have to be sought in the different ages of the lesions. Apparently typical of predominantly unilateral lesions of the upper or middle portion of the pons was bilaterally symmetric hypohidrosis of the trunk and extremities (cases 1 and 2). Ipsilateral hemihypohidrosis was found chiefly with lesions both of the lower pontile tegmentum and of the upper part of the medulla (cases 5 and 6), and also with a more orally situated vascular lesion (case 4). These experiences could be interpreted as suggestive evidence for a decussation of sweat fibers in the upper half of the pons, since bilateral hypohidrosis then may be explained by a unilateral lesion interrupting the crossing.

11. Papez, J. W.: Reticulospinal Tracts in the Cat, J. Comp. Neurol. **41**:365-399 (April) 1926.

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In more caudally placed lesions of the lower pontile tegmentum and the medulla oblongata, the sweating path may be destroyed below this presumable crossing, hence the ipsilateral hemihypohidrosis. Absence of complete anhidrosis in these cases may have to be attributed to incompleteness of the lesion or to the presence of fibers from the unaffected side crossing below the lesion. A normal sweating response of the face in cases of lesions of the oral pontile tegmentum seems to imply that the cephalic fibers form a special path. Our observations furnish no clue as to the position and physiologic properties of the hypothalamotegmental pathway, but they suggest that the reticulospinal connections conceivably may be of significance for sweating. In all observed cases of pontile lesions, the area occupied by the lateral reticulospinal tract was included in the lesion. In cases 1, 2 and 5 the medial reticulospinal tract presumably was involved on both sides, and in cases 1, 2 and 4 the ventral reticulospinal bundle also. It is worthy of note that ipsilateral hypohydrosis was found whenever the region of the already crossed lateral reticulospinal tract was destroyed in the caudal pontile tegmentum (below the level of the masticatory nucleus, cases 4, 5 and 6) and that lesions at the level of decussation of this path (cases 1 and 2) produced bilateral hypohydrosis. In cases 1 and 2 the presumable involvement of both medial reticulospinal paths and of the ipsilateral ventral reticulospinal tract may be of significance for the bilateral hypohydrosis; yet these predominantly unilateral lesions fail to explain the perfect symmetry of the sweating disturbance.

In the present literature there is no agreement as to the function of the reticulospinal tracts. Ranson [12] apparently concluded that they are efferent paths concerned with the mediation and correlation of somatic motor impulses from the brain stem to the cord. Gesell, Bricker and Magee [13] found evidence that the reticulospinal tracts play a role in the central regulation of respiration.

In the medulla oblongata the course of sweat fibers can be determined with greater accuracy, since our clinical material comprised cases of similar vascular lesions in which, with 1 exception, comparable sweating responses were shown. Ipsilateral hemihypohidrosis, which was only regional in cases of smaller lesions, was a typical finding with the sweating test. This tends to prove the interruption of an important ipsilateral sweating path which undergoes no major crossing below the

12. Ranson, S. W., in discussion on Peet, M. M., and List, C. F.: The Changes of Sweating in Lesions of the Pons, Medulla Oblongata and Cervical Cord, Tr. Am. Neurol. A. **64**:92-95, 1938.

13. Gesell, R.; Bricker, J., and Magee, C.: Structural and Functional Organization of the Central Mechanism Controlling Breathing, Am. J. Physiol. **117**:423-452 (Nov.) 1936.

lesion. The absence of complete anhidrosis, however, indicates that a lesser number of sweat fibers, especially those for the lower part of the body, are still functioning. It is conceivable that these intact sweat fibers pass through the more mesial and ventral parts of the medulla and thus were unaffected by the lesion, or one may assume that sweat fibers in the opposite (intact) half of the medulla cross below the level of the lesion. There is no certainty as to where such presumptive decussation occurs, but from experimental evidence (Karplus and Kreidl) and our own clinical observations it appears that these fibers cross at the level of the cervical region of the cord shortly before synapsing with cells of the intermediolateral gray matter. In this connection, the unusual case 11 may be mentioned, in which sweat fibers for the ipsilateral leg and paths for the contralateral arm and half of the trunk were interrupted while facial sweating was practically normal. In this case there is presented probably an anatomic variation, with a major crossing of sweat fibers for the contralateral arm and trunk somewhere below the level of the medullary lesion.

Some authors have concluded that contralateral hyperhidrosis in cases of medullary lesions was a sign of greater significance than ipsilateral hypohidrosis. We believe, however, that hyperhidrosis is here only a compensatory phenomenon and that the truly pathologic response consists of the diminished sweat secretion on the side of the lesion. This view is corroborated also by the usual observation of ipsilateral paresis of vasoconstrictor fibers and an ipsilateral Horner syndrome. In our cases of medullary lesion the region of the lateral reticular gray matter and the lateral reticulospinal tract was always affected, whereas the area occupied by the ventral and medial reticulospinal bundles probably had escaped destruction. It is therefore likely that the lateral reticulospinal tract contains sweat fibers. Whether the sweating pathway is actually identical with the lateral reticulospinal tract *sensu strictiori* (described by Papez in cats [11]) is uncertain, but it seems merely a matter of anatomic definition as to whether one wishes to call the sweat fibers a part of the lateral reticulospinal tract or assumes that they only accompany this pathway.

Clinical experience suggests that in the medullary region sweat fibers for various parts of the body possess a certain somatotopic arrangement. The marked ipsilateral hypohidrosis of the face and neck, demonstrable even with the smallest lesions (case 10), suggests that the cephalic sweat fibers form a distinct ipsilateral bundle in the lateral part of the medulla oblongata. Since hypohidrosis of the lower half of the body was apparently more marked with large lesions extending further mesially, the sweat fibers for the lower extremities may occupy a more medial position.

Except for the changes in perspiration, lateral medullary lesions invariably produce ipsilateral paresis of oculopupillary fibers (Horner syndrome) and of vasoconstrictor fibers. It may be noted that a Horner syndrome was absent in the cases of pontile lesions, except in 1 instance (case 6) in which the lesion undoubtedly extended into the medulla oblongata. Of interest again is case 11, in which an ipsilateral Horner syndrome and paresis of vasoconstrictor fibers of the face and neck were present, although sweating of these parts was not materially changed. This indicates that the course of oculopupillary and vasoconstrictor fibers usually is similar to, but not necessarily identical with, that of sweat fibers.

The similarity of sweating responses in cases of unilateral lesions of the cervical region of the cord and of the medulla oblongata suggests that the sweat fibers keep essentially the same arrangement in the cervical part of the cord as in the medulla. Since the disturbance of sweating after high cervical chordotomy is nearly as pronounced as in cases of the Brown-Séquard syndrome, it may be assumed that a major portion of the descending sweat fibers passes through or near the anterolateral tract, although there may be considerable scattering of fibers over the cross section of the cord. The moderate degree of hypohidrosis in the observations of the Brown-Séquard syndrome may be explained either by the incomplete character of the hemisection or by the assumption that some sweat fibers cross below the lesion. Total transverse lesions of the cervical part of the cord always completely abolish thermoregulatory sweating of the entire body.

According to Foerster,[14] the sweat fibers of the cervical region of the cord possess a somatopic arrangement in that the paths for the upper extremity pass through the innermost layers of the anterolateral and lateral tracts, whereas the fibers for the leg are more externally situated near the anterior borderline of the lateral pyramidal tract. Our experiences do not furnish sufficient information to support or refute this statement. Our observations tend to show, however, that the sweat fibers for the face and neck and also the oculopupillary path form a distinct ipsilateral bundle within the anterolateral tract. The course of vasoconstrictor fibers apparently is slightly different from that of sweat fibers in the cervical part of the cord, since in 1 instance (case 17) paresis of vasoconstrictor fibers was noted in one upper extremity whereas sweating was not disturbed.

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14. Foerster, O.: Symptomatologie der Erkrankungen des Rückenmarks und seiner Wurzeln, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1937, vol. 5, p. 1.

SUMMARY

Sweating disturbances are described in 18 patients with lesions of the pons, medulla oblongata and cervical part of the cord.

An anatomic outline is given of the pathways which connect the hypothalamus with the vegetative nuclei of the spinal cord and presumably serve to conduct impulses for thermoregulatory sweating.

Clinical experience suggests the presence of both crossed and uncrossed sweat fibers in the brain stem and probably also in the cervical part of the cord. There is evidence for a decussation in the oral half of the pons. Below the level of the distal end of the pons most descending sweat fibers remain ipsilateral; only a minority of fibers cross at lower levels before reaching the intermediolateral column of the cord. In individual cases variations as to the proportion of crossing fibers and the site of their decussation are shown. The descending sweat fibers pass through the tegmental region of the pons, the lateral reticular gray matter of the medulla and the anterolateral and lateral tracts of the cervical region of the cord. In the medulla oblongata most sweat fibers travel through an area occupied by the lateral reticulospinal tract, which may be the principal efferent path for thermoregulatory sweating.

Some observations indicate a somatotopic arrangement of sweat fibers in the medulla oblongata and cervical part of the cord. The central course of vasoconstrictor and oculopupillary fibers is similar to that of sweat fibers. In the medulla oblongata and cervical part of the cord the oculopupillary fibers travel in close association with the cephalic sweat fibers.

Case Reports

CEREBRAL CALCIFICATION IN A CASE OF CHRONIC PROGRESSIVE CHOREA

DANIEL M. LIPSHUTZ, M.D., SAN FRANCISCO

Pathologic infiltration of calcium in the central nervous system is not easily recognized symptomatically. The clinical picture ranges from absence of signs during life, with infiltration as an observation at autopsy, to milder symptoms of headache, dizziness and vomiting and to grand and petit mal attacks, which Geyelin and Penfield [1] called "cerebral calcification epilepsy," related to "endarteritis calcificans cerebri." Symptoms in which psychiatrists are particularly interested are the organic psychoses associated with such a pathologic process.

The problem of diagnosis in these cases is well demonstrated in the reports of Holschewnekoff,[2] Mallory,[3] Hansemann,[4] Bassoe and Hassin,[5] Lisa and Hirschhorn,[6] Pick,[7] Simon [8] and Jervis.[9]

The case of cerebral calcification reported here has both clinical and pathologic importance. Clinically, the case was repeatedly diagnosed as one of Huntington's chorea with psychosis. Pathologically, the changes were those fundamental in chronic progressive chorea, with additional secondary alterations due to the ischemia caused by obliteration and calcification of the vessels. A similar case was reported by Davidson, Goodhart and Shlionsky.[10]

From the Laboratory of Neuropathology of the New York State Psychiatric Institute and Hospital, New York.

1. Geyelin, H. R., and Penfield, W.: Cerebral Calcification Epilepsy, Arch. Neurol. & Psychiat. **21**:1020 (May) 1929.

2. Holschewnekoff, O.: Ueber Degeneration der Hirngefässe, Virchows Arch. f. path. Anat. **112**:552, 1888.

3. Mallory, F. B.: Contribution to the Study of Calcareous Concretions in the Brain, J. Path. & Bact. **3**:110, 1892.

4. Hansemann: Ein casuistischer Beitrag zur Verkalkung der Gehirngefässe, Verhandl. d. deutsch. path. Gesellsch. **2**:399, 1900.

5. Bassoe, P., and Hassin, G. B.: Calcification of the Cerebral Vessels, with a Clinical Picture Simulating Brain Tumor, Arch. Neurol. & Psychiat. **6**:359 (Oct.) 1921.

6. Lisa, J. R., and Hirschhorn, L.: Subdural Calcium Deposit of the Spinal Cord, Arch. Neurol. & Psychiat. **28**:416 (Aug.) 1932.

7. Pick, A.: Calcification of the Finer Cerebral Vessels with Remarks upon Its Clinical Significance, Am. J. Insan. **61**:419, 1905.

8. Simon, T.: Ausgedehnte Verkalkung der Hirngefässe bei einer Idioten, Virchows Arch. f. path. Anat. **55**:534, 1872.

9. Jervis, G.: Calcification in an Idiot, personal communication to the author.

10. Davidson, C.; Goodhart, S. P., and Shlionsky, H.: Chronic Progressive Chorea: The Pathogenesis and Mechanism; a Histopathologic Study, Arch. Neurol. & Psychiat. **27**:906 (April) 1932.

REPORT OF A CASE

The Central Islip State Hospital furnished the clinical record of this patient.

The patient, whose family history was without significance, was a white man aged 39, of Polish origin. It was impossible to obtain a history of the onset of the illness. He had been unable to work for more than a few days at a time for eleven years prior to commitment to the hospital (1932). He was described as having been quiet and good natured. It was evident, however, that he had been growing worse for the three years before his commitment. At times he seemed to be almost paralyzed. His disposition became irritable, and when angered he was uncontrollable.

Examination.—On admission to the State Hospital at Central Islip, N. Y., the patient showed choreiform movements of the entire body, marked lordosis and scoliosis, asthmatic bronchitis and an irreducible scrotal hernia on the right side. Laboratory examinations showed nothing abnormal.

Mental examination disclosed an organic type of involvement. The patient seemed well oriented for time and place, but memory for recent events was defective. It was difficult to ascertain the facts concerning memory for remote events, school and general knowledge, trends or hallucinations because of the difficulty of making adequate contact with the patient. Insight was lacking, and judgment was defective.

Course.—There was progressive exaggeration of symptoms. Four months after admission the patient experienced an epileptiform convulsion, lasting about five minutes. This seizure was repeated later on the same day, with increase in the pulse rate (156), temperature (107.8 F.) and respiratory rate (26). The patient died on the following day.

Pathologic Observations.—At autopsy the different viscera appeared essentially normal. The calvarium was thinned throughout. The occipital bone showed two areas of rarefaction. The pial vessels were congested, and the pia was milky, with subpial infiltration over the convexities and the base and marked pial proliferation in these areas. The brain showed marked atrophy, more so of the left hemisphere, and was soft to the touch. The basal vessels showed slight sclerotic thickening.

A horizontal section through the basal ganglia demonstrated more definitely the thinning of the frontal gyri and the widened sulci. The lateral ventricles were moderately dilated, the dilatation extending to the third ventricle. The choroid plexus appeared unaltered. The island of Reil showed similar atrophy of its substance. The putamen was entirely replaced bilaterally by a calcareous deposit, showing some extension into the corresponding caudate nucleus. The internal capsules appeared to be intact. The mesencephalon, pons, bulb and spinal cord showed no gross changes.

For demonstration of the finer histopathologic changes, the following methods were employed: the cresyl violet stain for ganglion cells, the Weil stain for myelin sheaths, the Davenport impregnation for axis-cylinders, the Holzer and Cajal gold chloride-mercury bichloride stains for astrocytes and the Dubrawski and Penfield methods for microglia and oligodendroglia. To facilitate cutting the calcified material, the Adrian [11] method proved useful.

Microscopic Study of Brain.—The frontal and parietal regions demonstrated more marked changes than did other areas of the cortex. The different cortical

11. Adrian, W.: Verbesserte Methode der Gelatineinbettung für Gefrierschnitte, Centralbl. f. allg. Path. u. path. Anat. **33**:201, 1922.

layers showed definite loss, of varying degree, of the small ganglion cells, more marked in the third and fourth layers. In some regions there was complete absence of these small ganglion cells, bare spaces being left between the large and the small pyramidal cells.

The small ganglion cells showed various phases of alteration. In a small number of cells approximately the normal size and shape were maintained, but

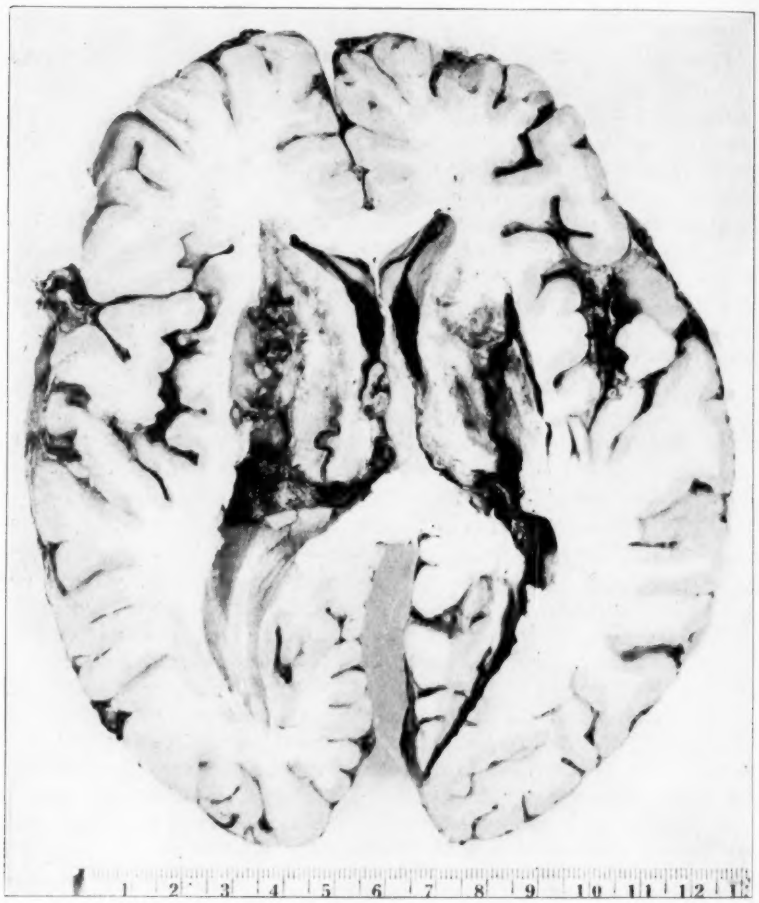

Fig. 1.—Horizontal section through the basal ganglia, demonstrating the bilateral infiltration of the putamen and part of the caudate nucleus.

the chromatin of the nucleus and the protoplasm of the cell showed a granular change. In a greater number the protoplasm assumed a homogeneous character, staining a diffuse blue with the dye. The cells contained many vacuoles, giving a foamy appearance to the protoplasm. The chromatin and the nucleolus had disappeared, leaving in the final stages a nuclear membrane which was irregular, thin and wavy, with strands of granular protoplasm attached to it. The small and large pyramidal cells maintained their normal cytologic architecture, but few

showed the normal tigroid bodies. A majority of cells of this type contained granular protoplasm, which appeared slightly swollen. A large number of the pyramidal cells were hyperchromatic and shrunken and showed little differentiation.

Almost all the white substance failed to stain with iron hematoxylin because of the diffuse process of demyelination. Only a few fibers stained with the dye, and these appeared fragmented, beaded and swollen. In marked contrast to the massive demyelination, the neurofibrils remained intact and were seen to continue into the peripheral layers of the cortex, where they tapered off to thin, fine strands, disappearing entirely before they entered the marginal layer.

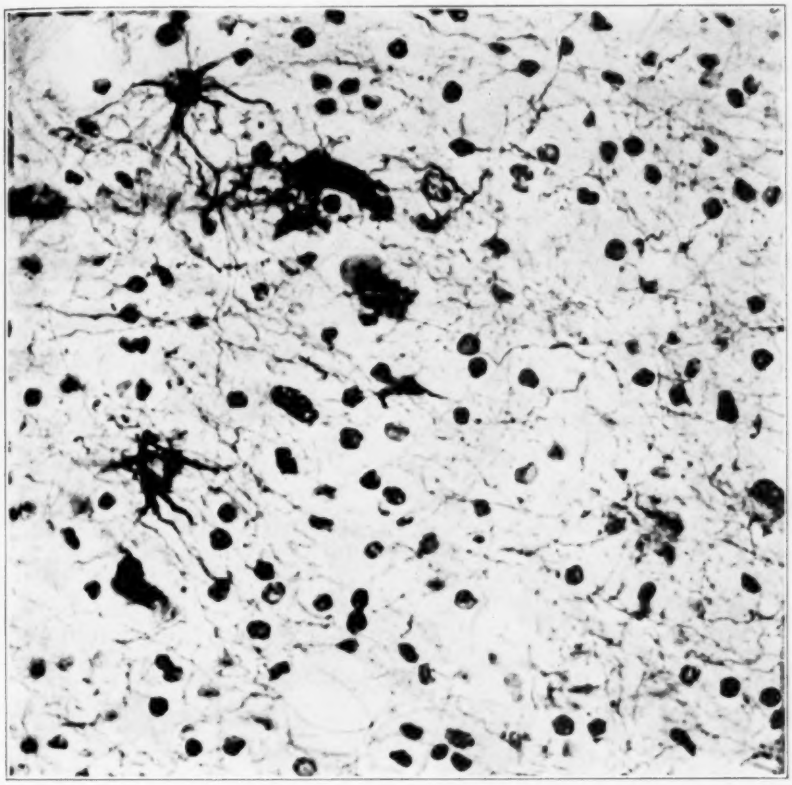

Fig. 2.—A Holzer stain showing hypertrophied astrocytes, many of which have undergone regressive changes. These are especially well demonstrated by the cells at the right of the photograph. × 540.

The actual condition of the neuroglial elements was demonstrated by the Holzer and Cajal stains. The astrocytes of the cortical layers and the subcortical white matter showed definite increase in number. Some had hypertrophied to the size of giant astrocytes, with multiple, thick fibrillar prolongations, which formed a network in the ground substance. Many of them had undergone regressive changes, as seen by retraction. With the Holzer stain the nuclei stained more deeply and showed retraction of the nuclear membrane, assuming an irregular form. In the

areas of the cortex showing calcification, these changes were more pronounced, giving a true picture of clasmatodendrosis.

A moderate increase of the microglia and oligodendroglia was present. The majority of the cells had multiple, granular, thick protoplasmic prolongations, containing large granules at their bases. This was more evident in the cells surrounding the ganglion elements.

In the lower layers of the cortex, adjacent to the subcortical white matter, a network of calcified capillaries stood out in relief. The changes in this level of the cortex varied in degree only, in contrast to those of the higher layers.

Fig. 3.—Alizarin S stain demonstrating the massive calcification of the putamen and caudate nucleus. The calcium appears black in the photograph, but is actually crimson in the slide, with purple hues about the periphery, depending on the amount of iron in the region. × 100.

The preparatory treatment with ammonia and sodium hydroxide dissolved the calcified substance about the vessels. The endothelium remained unaffected by the infiltration. The larger vessels of the subcortical white matter showed extensive involvement of the media. In some of them the media was entirely replaced by the solid ring of calcifying substance. Here, too, the endothelium

remained intact, but the adventitia contained an increased quantity of small spherules of the calcium-like substance, which was also present in the Virchow-Robin spaces.

A section through the calcified basal ganglia showed bilaterally a mass of homogeneous substance which stained deeply with all stains. The gray matter of the putamen and a large part of the caudate nucleus was almost entirely replaced by calcified substance. Only small limited areas still retained a semblance of nerve tissue, and these were largely filled with a network of calcified capillaries.

The transformation of the nerve tissue to complete calcification in this region was limited to the gray matter. In the internal capsules many small arteries and capillaries were affected, but the fiber bundles showed only slight demyelination, the neurofibrils remaining wholly intact.

A combination of the fat stains, the prussian blue stain for iron and the alizarin S [12] stain for calcium demonstrated the process of laying down and infiltration of the calcified substance. In nondecalcified sections the actual amount of iron present could be determined. The central core of the mass appeared to consist entirely of calcium compounds. The periphery of the mass had a varying amount of iron in combination. In the smaller spherules globules of fat were seen to form the central core, in and around which the iron and calcium compounds infiltrated. These small spherules appeared to become larger, coalescing with other adjacent masses to form one continuous mass of substance. When this was decalcified and stained the individual spherules were easily detected.

The cerebellum was infiltrated with calcium to an extent equal to that of the various areas in the cortex. The molecular layer was the one most often involved. The larger vessels here, too, showed similar calcification of their medial layers. The white substance showed extensive demyelination. The Purkinje cells for the most part remained intact.

The pons showed moderate demyelination of the corticopontile tracts, but the neurofibrils appeared normal. The demyelination was seen only at this level; it was not observed to continue into the lower levels of the brain stem or cord. These levels were free from the calcifying process.

COMMENT

Careful histopathologic investigation in this case points primarily to a degenerative type of alteration such as is found in chronic progressive chorea, previously reported by me [13] in a study of 12 cases of the disease. In the present case there were superimposed on the degenerative changes massive demyelination and changes in the ganglion cells, secondary to probable ischemia resulting from cerebral calcification. The degeneration of the striatum was almost entirely replaced by the calcifying substance.

Clinically, the symptoms were typical for Huntington's chorea with psychosis, as was pointed out in the patient's medical history. Epileptiform convulsions appeared one day preceding death. Clinically, the convulsions were the only atypical findings, suggesting a possible vascular complication associated with the calcifying process.

12. Cameron, G. R.: The Staining of Calcium, J. Path. & Bact. **33**:201, 1922.

13. Lipshutz, D. M.: Etude anatomo-pathologique des chorées chroniques, Rev. neurol. **66**:201 (Aug.) 1936.

In all reports on cerebral calcification the authors have agreed that some type of degeneration precedes the calcification. This idea is strengthened by the fact that in the cases reported in the literature in which calcification has been described there was frequently an abiogenetic factor in the history, a finding which would lead one to suspect the presence of constitutional predisposing factors. Thus, calcification has been found repeatedly in brains of idiots and persons with senile psychosis, less specific clinical entities showing familial trends and, more certainly, diseases of definite hereditary background, such as Huntington's chorea.

RESECTION OF LONGITUDINAL SINUS POSTERIOR TO THE ROLANDIC AREA FOR COMPLETE REMOVAL OF MENINGIOMA

GEORGE L. MALTBY, M.D., BOSTON

A recent instance of the operative removal of a large bilateral parasagittal meningioma with the conicident resection of a considerable portion of the middle and posterior part of the superior longitudinal sinus has been thought sufficiently important to warrant reporting, not only because of the lack of untoward effects on the patient but also because of the scarcity of similar incidents in the literature. Cushing and Eisenhardt,[1] in their recent monograph on meningiomas, made the following statement: "We know of only one instance in which a bilateral parasagittal meningioma along with involved sinus has been surgically removed from the rolandic area with no postoperative disability." This case was reported by David, Bissery and Brun [2] in 1934. Recently, Rowe [3] has reported another case of successful resection of the longitudinal sinus in the middle and posterior regions.

It has long been known that parasagittal meningiomas invade the sinus.[4] For many years it was believed that complete removal of tumor in sinus was impossible. Nevertheless, in recent years neurosurgeons have been successful in resecting larger and larger portions of the anterior part of the longitudinal sinus.[5] Extensive resections of the sinus, likewise, have been accomplished in the neurosurgical service of the Lahey Clinic, including removal of the frontal third, as well as resec-

From the Neurosurgical Service, the Lahey Clinic.

1. Cushing, H., and Eisenhardt, L.: Meningiomas, Springfield, Ill., Charles C. Thomas, Publisher, 1938.

2. David, M.; Bissery, and Brun, M.: Sur un cas de méningiome de la faux opéré avec succès: Absence de troubles paralytiques après résection du sinus longitudinal au niveau de l'abouchement des veines rolandiques, Rev. neurol. **1**: 725-730 (May) 1934.

3. Rowe, S. N.: Parasagittal Meningiomas, Am. J. Surg. **43**:138-141 (Jan.) 1939.

4. Cushing, H.: The Meningiomas (Dural Endotheliomas): Their Source, and Favoured Sites of Origin, Brain **45**:282-316 (Oct.) 1922. Towne, E. B.: Invasion of Intracranial Venous Sinuses by Meningioma (Dural Endothelioma), Ann. Surg. **83**:321-327 (March) 1926.

5. (*a*) Elsberg, C. A.: The Parasagittal Meningeal Fibroblastomas, Bull. Neurol. Inst. New York **1**:389-418 (Nov.) 1931. (*b*) Olivecrona, H.: Die parasagittalen Meningeome, Leipzig, Georg Thieme, 1934. (*c*) Tönnis, W.: Die Zulässigheit der Resektion des Langsblutleiters des Gehirns, Deutsche Ztschr. f. Nervenh. **136**:186-190 (March) 1926. (*d*) Vincent, C.; David, M., and Puech, P.: Méningiome de la faux du cerveau: Ablation de la tumeur intra et extracranienne; stérilisation, et remise en place du volet osseux; guérison, Rev. neurol. **1**:452-461 (April) 1931.

tions of the lateral sinus and torcular region. Among these cases there is, in addition to the one reported here, an instance concerning which brief comment should be made. In this case 2 inches (5 cm.) of the middle and posterior portions of the longitudinal sinus was removed in extirpating a parasagittal meningioma on the right side. Postoperatively, left hemiparesis developed, with hyperactive reflexes and a Babinski sign. This gradually improved, so that a year after operation it was in no way incapacitating and could be observed only on careful examination. The paresis in this case was due probably to unavoidable cortical trauma at the time of removing the large tumor and not to the coincident sinus resection, since the paresis was unilateral, the right arm and leg being normal. If this supposition is correct, there is contributed another case in which a large portion of the middle and posterior parts of the longitudinal sinus was resected without untoward effects. However, because of the motor weakness, which had not been present before operation, one cannot say unequivocally that at least some of the trouble may not have been due to the amount and location of sinus removed.

The consensus at present seems to be that it is extremely hazardous to resect the sinus posteriorly, most neurosurgeons believing that such resections should not be carried out posterior to the great rolandic veins. This opinion is borne out by various reports of disastrous results in surgical procedures of this nature.[6] Likewise, much was written in the records of war injuries about the effects of acute injury to the sinus,[7] and Waggoner [8] has described a syndrome of thrombosis of the rolandic vein. Yet in certain instances posterior resection of the longitudinal sinus is possible, as is shown by the case to be reported and by the case of David, Bissery and Brun,[2] as well as that of Rowe.[3]

This brings up the question as to when such a radical procedure is safe and the more theoretic problem of the physiopathologic background that makes resection possible without untoward results. It is believed that the slowness of occlusion of the sinus by tumor and the extent and efficiency of the collateral circulation which is established are the two most important factors. Tönnis expressed the opinion that any portion of a closed sinus may be resected if the obliteration has been present long enough and if one can count on an adequate collateral circulation. Rowe reiterated this opinion and stressed the importance of thrombosis of the sinus by tumor in order that adequate collateral circulation may be established. How is one to be sure of these factors? What are the exact course and nature of the efficient collateral circulation in the instances of successful excision? Until these questions are answered the margin of safety in resecting an involved sinus in the central and posterior thirds is still indefinite. It may be that detailed case reports of successful resections will add something to knowledge of the subject, and for this reason the details of the following case are presented.

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6. Olivecrona.[5b] Tönnis.[5c]

7. Holmes, G., and Sargent, P.: Injuries of the Superior Longitudinal Sinus, Brit. M. J. **2**:493-498 (Oct. 2) 1915.

8. Waggoner, R. W.: Thrombosis of a Superior Cerebral Vein: A Clinical and Pathologic Study of a Case, Arch. Neurol. & Psychiat. **20**:580-584 (Sept.) 1928.

REPORT OF A CASE

A judge aged 59 was referred by Dr. John Russell, of Putnam, Conn., on Aug. 27, 1938. His complaints at the time of admission to the New England Deaconess Hospital were disturbances of vision for the past year and a half, moderately severe headaches for the same period and, finally, awkwardness and weakness of the left leg for three months. He considered himself well until the onset of his present illness, except that ten years previously he had had "neuritis" in his left hand and arm, from which he recovered rapidly with local treatment. Visual symptoms one and one-half years before consisted of hallucinations in the form of flashes of light that seemed to turn off and on before his eyes. For this difficulty he was given glasses, but relief was not obtained.

About one year before admission he began to see newspapers with big headlines waving in front of him. These hallucinations appeared chiefly at night. He had visited several physicians since, and his visual acuity had grown slightly worse. In May 1938, some impairment of the left visual field was found, and at the same time severe headaches occasionally appeared. These had been slightly less severe in the six months prior to admission, but were chiefly vertical and occipital. They were not accompanied by nausea or vomiting. Three months before admission he began to drag the left leg and foot when he walked. The left arm and leg gradually became weaker and more awkward, and on numerous occasions he stumbled and fell. On a few occasions he had faint and "dizzy" spells.

General physical examination showed an obese, partly bald man, with several retained dental roots, and moderate hypertension (systolic 174 mm.; diastolic 100 mm.). Neurologic examination revealed mild mental deterioration, with impaired memory for recent events, and perseveration in speech. He had bilateral choked disks of about 2 D., left homonymous hemianopia with macular sparing, narrowing of the left palpebral fissure, paresis of the right sixth nerve, weakness of the left side of the face on involuntary motion, spastic hemiparesis of the left arm and leg and a fairly marked intention tremor of the left hand. No sensory changes were found.

A roentgenogram of the skull revealed bones of normal thickness and density, with a single, very large, bilateral vascular groove in the region of the coronal sutures. The posterior clinoid processes appeared thin; the sella was normal in size. A shadow lateral to the sella suggested the presence of calcified vessels. The pineal body was calcified, but was not well visualized in the anteroposterior direction.

On the fifth day following admission ventriculographic examination was planned, but on incision of the dura on the right a red, granular-appearing tissue was revealed immediately underneath. It was believed that this was a tumor, probably a meningioma. Since the growth was definitely localized by the burr hole, it was considered unnecessary to make air studies. On the same day, therefore, a right occipitoparietal craniotomy was performed by Drs. Gilbert Horrax and J. L. Poppen, with complete removal of a meningioma of this region, involving both the falx and the sinus. The tumor was pathologically verified as a meningioma; it weighed 125 Gm.

At the time of operation it was observed that the longitudinal sinus was involved by the tumor, and an area, at least 4 cm. in length, in the parieto-occipital region was excised. An abstract of the operative note follows.

"Finally the sinus was ligated anterior to its involvement by the tumor, a total of at least 4 cm. being excised in the parieto-occipital area. We had not attempted to do such a resection in this region before, but it seemed necessary

in this case in order to get rid of the tumor completely; it remains to be seen, therefore, what the effect on the patient's motor function may be. Anteriorly, at the point where the sinus was ligated, a nubbin of growth was drawn out of the sinus, and the sinus in this area was sucked free of tumor and then coagulated until free bleeding occurred."

The entire operation was a bloody affair. The patient was given two transfusions during its course, and at the end of the procedure was in fair condition. The reaction, considering the magnitude of the operation, was moderate The temperature returned to normal on the eighth postoperative day. Daily aspirations of from 10 to 30 cc. of fluid from under the scalp were carried out. On the twelfth postoperative day the patient was allowed to sit up in bed and on the thirteenth day was allowed up in a chair. However, on the twentieth day his temperature again became elevated, and on the twenty-first day it reached 102 F., with a definite area of redness over the posterior part of the incision and over

Lateral view of the skull, taken postoperatively, showing the bone flap in place. The arrows point out the clips marking the anterior and posterior limits of the portion of the longitudinal sinus that has been resected.

the ventriculographic opening on the right side. On spinal puncture no organisms were found, however, and the temperature gradually receded with repeated aspirations. He was discharged on the fortieth postoperative day.

Examination at the time of discharge showed the patient to be somewhat unsteady on his feet, with slight spasticity of the left side, but on the whole he walked well, considering the length of time that he had been in bed. The unsteadiness seemed to be the result more of weakness than of actual neurologic difficulty. The scar on his head had healed well, as had the incisions for ventricular taps. He still had moderate left hemiparesis and a few nystagmoid jerks on looking to the left. Examination of the fundi showed that the right nasal border was slightly hazy but that both cups were returning. The appearance of the fundi was that of subsiding papilledema. There were some tremor on extending the hands, slightly greater on the left than on the right, and slight ataxia in the finger to nose test; the reflexes on the left were greater than those on the

right. He had definite trouble in stepping up or in getting into bed. However, the examiner believed that this was no worse, and probably slightly better, than it was prior to the operation. The left arm was definitely improved, being much stronger and less spastic than it had been. The upper left abdominal reflex was absent; the knee and ankle jerks on the left were greater than those on the right; there was some unsteadiness in the heel to shin test on the left; position and vibratory sense were slightly diminished in both legs, and the left plantar response was equivocal, but not definitely pathologic. Visual acuity was normal, being 20/15 in the left eye and 20/20 in the right eye. There was still left homonymous hemianopia with slight macular sparing.

Roentgenograms of the skull were taken at the time of discharge from the hospital. They showed definitely the extent of sinus removed, since it was known that a group of silver clips had been placed at the anterior and the posterior limit of excision (figure). From these clips it is obvious that considerably more than 4 cm. of sinus must have been resected. The distance was more nearly 6 or 8 cm.

It was extremely interesting to see that motor dysfunction did not increase. In fact, at the time of discharge the patient's condition was definitely improved as compared with that before operation.

SUMMARY

An instance of extensive resection of the longitudinal sinus posterior to the rolandic vein during the removal of a parasagittal meningioma has been reported. This was accomplished without any untoward postoperative effects. The literature concerning operative excision of the longitudinal sinus has been briefly reviewed. It is believed that the study of detailed reports of cases in which the posterior longitudinal sinus has been successfully removed will improve the neurosurgeon's ability to judge when such procedures are safe.

Obituaries

HARVEY WILLIAMS CUSHING, M.D.
1869–1939

On Oct. 7, 1939 died after a brief illness Harvey Williams Cushing, one of the most distinguished surgeons of his generation. He was born on April 8, 1869, in Cleveland, of New England stock, the son, grandson and great grandson of physicians. After his preliminary education in Cleveland, he entered Yale College and later Harvard Medical School. He interned in the Massachusetts General Hospital and later went to Johns Hopkins Hospital for four years of postgraduate work (1896-1900).

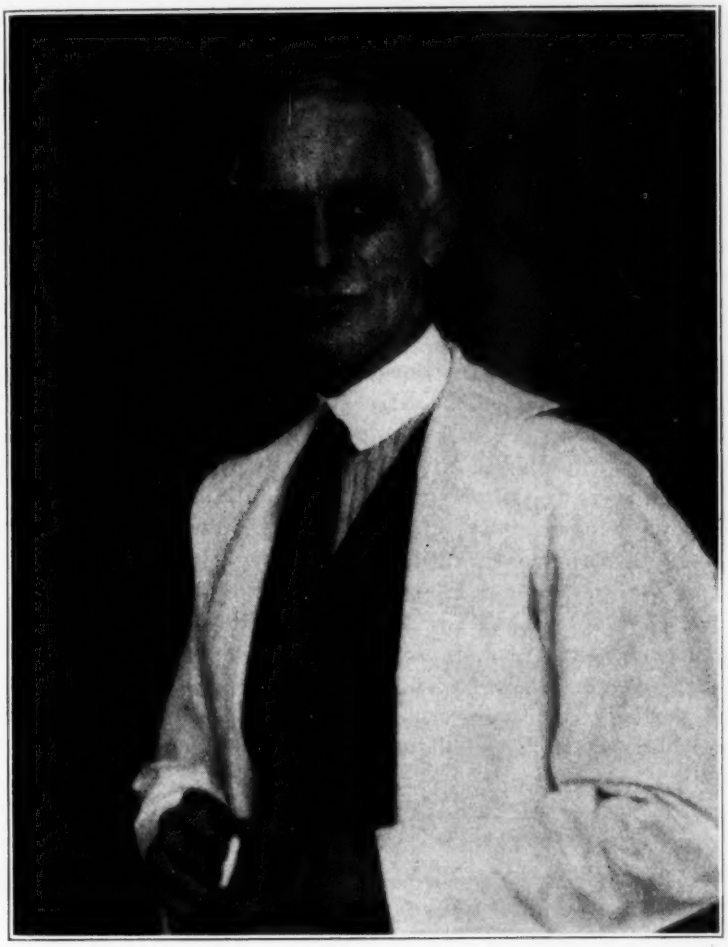
In 1900-1901 he studied abroad. First he visited Horsley, for he was already inclined toward intracranial surgery. Not finding the proper stimulus from this busy man, he moved on to Berne, Switzerland, where the surgeon Kocher put him to work in Kronecker's physiologic laboratory investigating the effect of increasing the intracranial pressure. He made an excellent study, establishing the fact that an elevation of the cerebrospinal pressure causes a compensatory rise of the blood pressure; this was the subject of a Mütter Lecture at Philadelphia on his return. After a brief period in Italy he returned to England, where Sherrington welcomed him at Liverpool and he spent some happy months working with that great physiologist, who was then investigating the motor cortex of the anthropoid apes.

Home again in Baltimore, Halsted put him in charge of the Hunterian Laboratory. Here was an opportunity to continue experiments which were also good training for the budding brain surgeon. Paulesco had maintained (1906) that the hypophysis was essential to life. Cushing began to repeat the experiments of Paulesco, at first agreeing with him, but later he was fortunate enough to observe that the hypophysectomized animals did not always die but might develop an adiposogenital dystrophy. This observation, plus a successful operation on Gen. Leonard Wood in 1910, resulted in his being chosen Moseley Professor of Surgery at Harvard.

The two men in Baltimore who influenced him most deeply were Halsted and Osler. From the former he got his fastidious technic, from the latter a humanitarian bent. From Osler also he acquired a love for books and for literary pursuits. By patient effort he attained an excellent literary style, which enabled him to win the Pulitzer prize for the biog-

raphy of his teacher and friend. His magnificent collection of books he afterward left to his alma mater.

The outbreak of the World War found him eager to broaden his experience and to lend his skill to the allied armies. He first entered the British army and then, after the entry of the United States into the war,



HARVEY WILLIAMS CUSHING, M.D.
1869-1939

headed Base Hospital No. 5. Some of his experiences in that great struggle he published as a book, entitled "From a Surgeon's Journal" (1936). It was during this time, also, that he fell ill with a polyneuritis from which he never fully recovered his physical energy, although the driving force of his personality was undiminished.

After his return to Harvard began the brilliant period when his reputation attracted pupils to him from all over the world. The Peter Bent Brigham Hospital became the Mecca of physicians interested in neurosurgery. His work and influence during this time established neurosurgery on a sound foundation.

When he reached the age limit and was obliged to retire from his professorship, he ceased to operate and began a quieter period as Sterling Professor of Neurology at Yale (1933). Here his pupils would drop in and talk with him more intimately than it was possible for them to do when he was overburdened with clinical work. This period of relative leisure enabled him to complete his monumental monograph on meningeal tumors. On his seventieth birthday his pupils gathered to celebrate with him. A more perfect occasion it would be difficult to imagine. No one present can ever forget that evening, for many the last opportunity to see our chief. Shortly afterward he suddenly passed away.

This is no place to recount his honors and accomplishments. The list would be too long, and is readily available in the bibliography published by the Harvey Cushing Society. Few have brought greater honor to their country or profession. His position in the history of medicine is assured.

He developed slowly. His academic record in Yale College and Harvard Medical School was undistinguished. Not a reflective type, it was not until he reached the clinic that his genius became apparent. Then he blossomed immediately, when a field for action appeared. His artistic sense, his motor skill, his tenacity of purpose, his dogged perseverance, his absolute assurance, his ruthless determination, his ascetic self denial, his stoical endurance, his theatrical flair—all made him the peerless surgeon. Every one must agree that he was the dominant force in the creation of modern neurosurgery. And he had a "nose" for anything which would help him in his task. The sphygmomanometer, sewing silk, roentgen rays, hypertonic solutions, electrical scalpel—these and many other aids he gathered promptly on his way and turned to his own purpose.

In the scientific field, he made a great contribution to endocrinology. His production of the syndrome of adiposogenital dystrophy in the experimental animal gave such an impulse to research in this field that it has not yet spent itself. After thirty years of study the syndrome he produced is still not entirely understood, but a host of other things are clearer for the effort.

During the years when I worked with him (1919-1928) his attention was concentrated on tumors of the brain. He rarely visited the experimental laboratory and took little part in what went on there. He had already the foresight to realize that the histories of his patients must be followed to the end. Also he felt that intracranial tumors were too

heterogeneous to be studied profitably as a group. Not having the training in pathology needed for the isolation of types which might be studied individually, he had attempted to interest pathologists in the problem, without much success. It was the creation of a special laboratory for the completion of this task which he persuaded me to undertake in 1922. One result was the classification of gliomatous tumors, which has since caused so much ink to flow. After my departure in 1928, this laboratory was carried on by Dr. Eisenhardt, who for many years had kept the follow-up records of his patients and who became the director of the Cushing Brain Tumor Registry, which he later founded at Yale (1933).

Although Cushing maintained that a neophyte should approach neurosurgery through general surgery, and was the head of a general surgical service for twenty years, he was interested almost exclusively in his own cases of brain tumor and rarely attempted to operate on anything other than intracranial or intraspinal lesions. His belief in the necessity of a long training in general surgery as a preparation for neurosurgery was finally shaken by the success of Clovis Vincent, as he once admitted to me. Because of his insistence that the surgeon must be able to see all around his problem and make his own decisions, he felt his own lack of neurologic training, which led him sometimes into error. It is quite understandable that there should be defects in the equipment of a man who was feeling his way tentatively while creating a new field of surgery. He saw the needs and did his best to supply them by surrounding himself with men, like the ophthalmologist C. B. Walker, who could bring him skill he lacked. But he instinctively warded off the medical neurologist, who would have reduced him to the level of a technician, and strove instead to acquire for himself the neurologic knowledge needed for his work. This enabled him to make contributions in the general neurologic field, for example, his studies on the visual system.

No less important than his contributions to medicine were the results of the impact of his personality on his numerous pupils. Wherever civilized medicine was practised his influence was felt. Pupils came to him in ever increasing numbers. My own debt to him is incalculable. It would need a volume to discuss all the lessons he taught me, and all the others he tried to teach me which I did not grasp at the time. I was with him, off and on, for nearly ten years. He was not an easy man to work with. We disagreed often, sometimes vigorously. When the tension became too great I went away for a while. But I always came back. And when I did there were neither apologies nor reproaches on either side. We simply began again where we had left off. To account for these clashes would be to attempt an appraisal of the man and his work. This is not the time for such an attempt, were I presumptuous

enough to undertake it. Posterity will inevitably make such an evaluation. In the meantime the shadow of his dominant personality beclouds judgment. But his pupils are persuaded that his ultimate rank will be very high.

He was a man of intense personal magnetism. He either repelled men or attracted them; it was impossible to be indifferent toward him. His sudden death was a bitter sorrow to me, for I had with eager anticipation planned to spend several months with him again. I saw him seldom in the later years of his life, but his spirit was always with me. I am conscious mainly of a great void. A major force for good in American medicine has been suddenly throttled, but it will be long before his powerful influence has spent itself. His imprint is indelibly stamped on all of his disciples, as he wished it to be. He has departed, and we must continue his work. Few indeed will have faults as recessive and virtues as dominant as were those of the man whom we are proud to call our master—HARVEY CUSHING.

PERCIVAL BAILEY, M.D.

Abstracts from Current Literature

Neuropathology

CEREBRAL VASCULAR DISEASE ACCOMPANYING SICKLE CELL ANEMIA. W. H. BRIDGERS, Am. J. Path. **15**:353 (May) 1939.

A clinical and pathologic study of 2 cases of sickle cell anemia accompanied by symptoms of cerebral vascular disease is reported on by Bridgers because of its contribution to the pathogenesis of the disorders of the central nervous system associated with this disease. The 2 cases show that sickle cell anemia may first become manifest through the appearance of signs and symptoms indicative of cerebral vascular disease. The clinical features in such cases lead to the diagnosis of either cerebral vascular thrombosis or intracranial hemorrhages. The pathologic changes seen in 1 of the cases establish the fact that in sickle cell anemia the large subarachnoid cerebral arteries may undergo gradual obliteration with final complete closure through the operation of a process identical with that which results in occlusion of the splenic arteries. This process is one of endarterial intimal proliferation, and not of thrombosis. In the second case necropsy showed that another vascular process, quite different from endarterial intimal proliferation, also occurs in sickle cell anemia. This process develops in connection with the small intracerebral vessels and may result in multiple focal necroses and hemorrhages in the brain, in contrast to the large infarcts that characterize the proliferative obstructive process in the larger arteries. The nature of this second process is not clear.

J. A. M. A.

EXPERIMENTAL PRODUCTION OF TUMORS OF THE BRAIN WITH THE SHOPE RABBIT PAPILLOMA. BARNES WOODHALL, ROBERT W. GRAVES and J. W. BEARD, Arch. Surg. **38**:457 (March) 1939.

The authors produced intracranial tumors experimentally in rabbits by extradural and subdural implantation of the cutaneous papilloma induced by the virus of infectious papillomatosis. The intracranial growths were similar in gross characteristics to those observed after transplantation of the papilloma in other organs and in other tissues of the rabbit. In contrast to the behavior of the growth on implantation in other tissues, with the possible exception of the kidney and stomach, there was inability of the proliferating epithelium to invade adjacent tissue. When even a thin layer of meninges lay between the tumor and the brain there was a minimum of glial reaction. On the other hand, whenever the tumor came in direct contact with the brain there was astrocytic proliferation with the formation of numerous fibers, many of which were attached to the tumor. Where such gliosis was heaviest there was increased vascularity, and thrombosis occasionally occurred, producing localized areas of necrosis with microglial reaction.

GRANT, Philadelphia.

LYMPHOCYTIC CHORIOMENINGITIS: ISOLATION OF THE VIRUS FROM THE NASOPHARYNX. F. O. MACCALLUM and G. M. FINDLAY, Lancet **1**:1370 (June 17) 1939.

In examining material from patients with acute symptoms suggesting involvement of the nervous system, MacCallum and Findlay isolated the virus of lymphocytic choriomeningitis in 4 cases. In the case they describe the original diagnosis made on clinical grounds was acute anterior poliomyelitis, but the virus of lymphocytic choriomeningitis was isolated from the cerebrospinal fluid once and from nasopharyngeal washings twice. The isolation of the virus of lymphocytic chorio-

meningitis on three separate occasions from the same patient and the failure to incriminate the virus of poliomyelitis indicate to the authors that the virus of lymphocytic choriomeningitis was responsible for the clinical condition. The possibility of a double infection must be considered, but as the nasopharyngeal washings failed to yield evidence of the virus of poliomyelitis there is no experimental proof of its being present. The virus was still present in the nasopharynx eight and twelve weeks after the onset of the illness. Failure to demonstrate neutralizing antibodies in the serum eight weeks after the illness started could, the authors state, be taken as evidence against the specificity of the infection, but the slow development of antibodies in patients infected with this virus has been stressed by Scott and Rivers and by Howard. The data in the present case suggest that the virus of lymphocytic choriomeningitis is probably present at some period in the nasopharynx of patients suffering from this infection. It may possibly be present in the same situation in healthy carriers and in persons suffering from febrile symptoms without definite involvement of the nervous system. There is need for renewed study and interest in the cause of acute infections of the central nervous system of unexplained origin. The virus of lymphocytic choriomeningitis should be searched for not only in cases of conditions clinically resembling acute aseptic lymphocytic meningitis but also in those of other acute nervous and febrile complaints of unknown origin.

J. A. M. A.

PSYCHOTIC FORM OF EPIDEMIC PAROTITIS. C. I. URECHIA, Encéphale **2**:144, 1938.

Only 12 cases of epidemic parotitis with necropsy have been reported. In only 4 of these was the brain examined microscopically. The lesions consisted of hemorrhage, congestion, mild perivascular infiltration with lymphocytes, patchy demyelination, formation of glial nodules and meningitis. These lesions were not all present in each case. In 1 case only congestion of the parenchyma and slight meningeal infiltration were shown. The present report concerns a woman aged 54 who suffered from acute confusion and mania, with logorrhea, agitation, flight of ideas, incoherence, unsystematized ideas of persecution, anxiety and anorexia. This state lasted for five days before the appearance of bilateral parotitis. The pulse rate was 120. There was no fever. The patient died with signs of heart failure seven days after onset of the mental symptoms and seven days after onset of the parotitis. The brain was congested and edematous. Along the fissures were streaks of meningitic involvement. Microscopically there were patches of discrete infiltration with lymphocytes and plasma cells, and small hemorrhages in the meninges. The cerebral cortex presented discrete cellular lesions of the acute type of Nissl, chiefly in the superficial three layers. There was no degeneration of myelin or axons. The ganglion and glia cells contained abundant fat. In 2 other cases of mumps there was also psychosis at onset and death was associated with myocarditis.

LIBER, New York.

PARAPLEGIA IN FLEXION OF CEREBRAL ORIGIN: REPORT OF A CASE. NATHALIE ZAND, Encéphale **2**:151, 1938.

A woman aged 57 had pains in her right leg, followed by flexion contraction of the left arm. Three years later pain appeared in the left leg, and the entire body became rigid, with all extremities strongly flexed and the head turned to the right. The left side of the body was more involved than the right. The patient became apathetic and rapidly unconscious. Death occurred in three weeks. The brain showed multiple lacunas of disintegration in both cerebral hemispheres. The cerebral cortex appeared moth eaten in places. Microscopically, there were perivascular rarefaction and cavitation. The ganglion cells of the cerebral cortex, the central gray nuclei, the dentate nucleus, the nuclei of the pons and the bulbar olives showed extensive changes. There was marginal gliosis. The blood vessels presented marked proliferation of the internal elastic fibers, but no inflammatory phenomena. Jakob concluded that a lesion of this type was chronic syphilitic arteri-

tis. The flexor position of the paralyzed extremities can be explained by the degeneration of the olive. In cases of lesions of the precentral gyrus or its projection fibers the reflex postural mechanism of the olive is released. This results in extension of the lower extremities. But if the olive is also injured the spinal reflexes are released, giving rise to flexion. The pain in this case may be explained by the lesions in the thalamus.

LIBER, New York.

CEREBROCUTANEOUS MELANOBLASTOMATOSIS. R. LECOUTURIER, J. LEY, J. TITECA and L. VAN BOGAERT, J. belge de neurol. et de psychiat. **39**:103 (Feb.) 1939.

The authors report the case of a boy aged 3 who had numerous pigmented nevi over the body from the time of birth and who experienced convulsive seizures, vomiting and signs of progressing hydrocephalus in the second month. The clinical diagnosis was metastatic tumor in the posterior fossa, but postmortem examination revealed diffuse involvement of the meninges, cerebellum and brain stem by a melanoblastomatous growth. The authors believe that the association of multiple cutaneous nevi with diffuse involvement of the nervous system signifies that the abnormality is congenital, with simultaneous involvement of various tissues which arise from the ectoderm.

DE JONG, Ann Arbor, Mich.

NEUROPATHOLOGIC LESIONS IN THE DOG. H. J. SCHERER and L. COLLET, J. belge de neurol. et de psychiat. **39**:132 (Feb.) 1939.

Recent reports on pathologic changes in the nervous system of the dog have dealt principally with those occurring in canine distemper, and have stressed this variety of diffuse encephalomeningitis as the only disease of the nervous system of importance in dogs. Scherer and Collet report 3 cases of spontaneous disease of the brain in dogs which resembled each other clinically, but differed greatly pathologically. In 1 instance there was intense, diffuse intracortical vascular proliferation; in another case disseminated cerebral lesions resembled multiple sclerosis, without evidences of infiltration or meningeal reaction, and in the third there was advanced diffuse sclerosis. The authors do not believe that the histopathologic picture of distemper is sufficiently well defined to permit the view that it is a specific disease entity.

DE JONG, Ann Arbor, Mich.

RELATION OF THE MAMILLARY BODY TO KORSAKOFF'S SYNDROME. E. GRÜNTHAL, Confinia neurol. **2**:64, 1939.

Grünthal states that the mammalian mamillary body is not one of the hypothalmic vegetative centers but is a special organ, connected in man by way of the anterior nuclei of the thalamus with those portions of the frontal cortex which lie immediately in front of the motor cortex. He reports in detail a case, clinically diagnosed as an instance of Korsakoff's psychosis, in which there was circumscribed destruction of the mamillary bodies. He believes that these structures may be of importance in regulating certain psychic functions, especially those related to repression and inhibition.

DE JONG, Ann Arbor, Mich.

CIRCUMSCRIBED ARACHNOID SARCOMA OF THE CEREBELLUM. O. FOERSTER and O. GAGEL, Ztschr. f. d. ges. Neurol. u. Psychiat. **164**:565 (Jan.) 1939.

Three arachnoid sarcomas of the cerebellum were encountered in a series of 600 histologically verified tumors of the brain. Each of the sarcomas was located on the surface of the cerebellum, leaving a flat indentation when removed. The tumors infiltrated the brain only along the Virchow-Robin spaces. There were no connections with the dura. They were friable, irregular and of somewhat harder consistency than the brain. There was no capsule and no tendency to the formation of cysts. In 1 tumor there was some spread of malignant cells to the

neighboring leptomeninges. Two types of cells were crowded together in rows and islets: small cells, rich in chromatin and resembling lymphocytes, with hardly any protoplasm, and large cells with a paler nucleus and with less deeply staining chromatin. Mitoses were seen. There was a rather marked reticular network in 2 cases. In 2 cases the tumor was on the dorsal surface, and in 1 case on the lateral surface of the cerebellum.

All 3 patients were in the third decade of life, the ages being 22, 23 and 25 years, respectively. The course was rapid in all cases, varying from a few weeks to six months. In a fourth case the tumor was successfully removed; the patient was still alive three months after operation. In all cases occipital pain was marked; there was forced extension of the head; any attempt to move the head resulted in marked intensification of the occipital pain. There were definite signs of cerebellar involvement in all 4 cases, more marked in the homolateral upper limb. In 3 cases there was definite limitation of conjugate gaze toward the side of the lesion, with coarse nystagmus in each instance. In 2 cases there were spasms of conjugate gaze toward the side of the lesion. In 1 case so-called cerebellar fits were noted. Vomiting occurred in 2 cases. Choked disk was present in 2. Dizziness was reported in only 1 case. In 1 case irregularity of the pulse rate, marked bradycardia and hyperhidrosis accompanied exacerbations of the occipital pain. In another case the pulse became very slow during attacks of vomiting. In 2 cases there were recurring periods of clouding of the sensorium, and even deep coma. In 3 of the 4 cases death was due to respiratory paralysis.

SAVITSKY, New York.

HISTOLOGIC CHANGES IN THE BRAIN STEM IN TUMORS OF THE CASES OF CEREBELLOPONTILE ANGLE. G. DÖRING, Ztschr. f. d. ges. Neurol. u. Psychiat. **165**:256, 1939.

In order to study the possible causes of the high mortality following apparently successful operations for tumors of the angle, the pons and medulla oblongata were investigated histologically in 15 cases, in 12 of which there were acoustic neuromas and in 3 extrapontile neoplastic processes. Degenerative changes, probably of retrograde nature, were often observed in the facial nucleus. The number of cells in the ventral cochlear nucleus varied greatly and depended on the degree of atrophy of the cochlear nerve. In the nucleus triangularis dorsalis vestibularis degenerative changes were rare and usually involved the larger cells. The histologic changes corroborate the opinion that the cochlear nerve is more vulnerable to pressure than the vestibular nerve. The facial nerve is even less sensitive to pressure. Disturbances of the fifth nerve are not prominent or marked in cases of acoustic neuromas. Changes in the fifth nerve associated with acoustic neuromas are due usually to pressure on the descending root, either on the same or on the opposite side of the brain stem. The author presents a photograph showing degeneration in both descending roots in a case of tumor of one angle only. Sensory changes in parts of the body other than the face were rare. They were found in 4 cases. Pain and temperature sensations were most often involved. These sensory changes usually appeared late and sometimes were absent even in cases in which there was marked deformation of the brain stem. Involvement of the ninth, tenth and twelfth cranial nerves was much rarer and less marked, though histologic study of the roots and nuclei of these nerves showed changes which probably accounted for the unexpectedly poor results following operative intervention. Significant changes were seen in the dorsal and ventral vagal nuclei, the hypoglossal nucleus and the nucleus intercalatus. The changes in the hypoglossal nucleus were least marked. The most important changes were in the dorsal and ventral vagal nuclei. Changes in these cell groups were noted with almost all larger tumors of the angle compressing the brain stem. The cells were larger than normal and showed breaking up of the Nissl substance.

SAVITSKY, New York.

CHRONIC RHEUMATIC DISEASE OF THE BRAIN AS A CAUSE OF MENTAL DISEASE. WALTER L. BRUETSCH, Ztschr. f. d. ges. Neurol. u. Psychiat. **166**:4 (March) 1939.

Bruetsch believes that chronic rheumatic infection of the brain probably plays a role in accounting for some cases of mental disease. He found rheumatic heart disease in 4 per cent of 475 patients with mental disease on whom autopsy was performed. In all cases significant histologic changes were observed in the brain. Bruetsch believes that the pathologic changes were due to rheumatic infection. The clinical pictures were: dementia praecox, manic-depressive psychosis and involutional and senile psychoses. In 2 elderly patients the diagnosis was psychosis with cerebral arteriosclerosis. One case was that of mental deficiency with a psychotic episode. In most of the cases rheumatic endarteritis was observed, involving especially the pial and cortical vessels. Many small and large areas of cerebral softening were seen. In 2 cases meningoencephalitis rheumatica was present in patients with transitory mental changes during the involutional period. Bruetsch answers Bodechtel's objection that similar changes were present in the brains of persons with rheumatic heart disease without mental symptoms by pointing out that the anatomic changes in the patients with the psychoses were much more extensive and severe.

SAVITSKY, New York.

Psychiatry and Psychopathology

PATTERN FEATURES AND CONSTITUTIONAL SUSCEPTIBILITY AS RELATED TO ORGANIC BRAIN DISEASE, WITH SPECIAL REFERENCE TO GENERAL PARALYSIS. BEATRICE POSTLE, J. Nerv. & Ment. Dis. **89**:26 (Jan.) 1939.

Postle reports 4 cases in which patients who had already suffered from psychotic attacks subsequently had dementia paralytica. In all the cases the psychosis during the period of dementia paralytica was identical with the previous mental disturbance. In 3 instances the psychosis was depressive, and in 1 of these agitation and delusional ideas were prominent. In the fourth case the clinical manifestations were clearly schizophrenic. In 1, that of an agitated depression with delusions, two psychotic episodes of identical character occurred after the dementia paralytica had been successfully treated and the reactions in the blood and cerebrospinal fluid had returned to normal. Postle concludes that the mental symptomatology in organic disease of the brain is a function of previous personality tendencies and not of the location of the disease process.

MACKAY, Chicago.

FEELINGS OF UNREALITY AND DISPLACEMENT. ANNETTE C. WASHBURNE, J. Nerv. & Ment. Dis. **89**:37 (Jan.) 1939.

Washburne proposes the theory that feelings of unreality are due to a failure in the mechanism of displacement. Attainment of the primary love object having been blocked, an attempt is made at displacement of libido toward a substitute goal. When this also fails, the environmental rapport of the patient is so disturbed that there are regression and inability to make any adjustment whatever. Feelings of unreality, either of self or environment, may result. The author admits that so simple a theory can hardly be more than a fraction of the whole answer.

MACKAY, Chicago.

THE PSYCHOLOGY OF METRAZOL TREATMENT OF SCHIZOPHRENIA. PAUL SCHILDER, J. Nerv. & Ment. Dis. **89**:133 (Feb.) 1939.

Schilder reports his observations on 20 patients with schizophrenia treated by metrazol shock. The therapeutic results in cases of the acute form in which the

disease had lasted less than six months were uniformly excellent. In most cases the improvement came after the second or third convulsion, and symptoms disappeared after the fifth or sixth. After the convulsion, consisting of tonic and clonic phases, a period of flaccidity with diminution or absence of tendon reflexes supervened, followed by changing rigidities and later by pathologic plantar responses. Coma then passed into confusion and restlessness, and during this period a friendly reaction to the physician or nurse appeared, at first clumsy but later more articulate. This friendliness occurred irrespective of sex; heterosexual reactions were more outspoken, and sometimes took the form of actual advances toward persons of the opposite sex. The confusion of this period was manifested by aphasic disturbances, perseveration and inability to copy simple gestalt patterns, which was proportional to the aphasia and disappeared from one-half to one hour after the convulsion. There was a tendency to revert to primitive gestalt principles, indicating a deep organic disturbance of the form function, unlike the disturbances observed in schizophrenia. Of the clinical manifestations, catatonic symptoms disappeared first, while paranoid ideas paled and disappeared more gradually. This change was associated with lessened tension, increasing amiability and friendliness and a gradually deepening transference to the physician. An objective insight finally developed, which included the realization that hallucinations and delusions had been experienced, but without knowledge of the psychodynamics underlying these experiences. Even in unsuccessfully treated patients improvement in mood occurred.

Schilder concludes that the aura and convulsion produced by metrazol constitute a fundamental threat of annihilation and death, and that an enormous feeling of relief follows emergence from the attack, setting free the patient's psychic energy once more. Previous fixations of libido have lost their importance, and there is renewed interest in persons near the patient. Thus, an emotional reorientation of the patient becomes possible. Though this is a psychologic interpretation, Schilder believes that metrazol shock acts not "as a psychologic agent in the common sense," but as an organic process which becomes reflected in psychologic attitudes.

MACKAY, Chicago.

ROLE OF HEREDITY IN STUTTERING. S. E. NELSON, J. Pediat. **14**:642 (May) 1939.

Nelson compared the lineage histories of 204 stutterers with those of 204 nonstutterers. The subjects of both groups were matched in age and sex. Those belonging to the stuttering group were selected only because they stuttered; those belonging to the control group were selected because they spoke normally and had no history of stuttering. Additional information was secured from grandparents, aunts, uncles and friends. The trend of the data seems definitely to indicate that there must be some biologic tendency to stutter. The conclusions pointing to that tendency are as follows: A greater percentage of stutterers who have ancestral pedigrees of stuttering began to stutter when they were learning to speak, while a greater percentage of the stutterers whose pedigrees show no ancestral stuttering began to stutter after the onset of speech. There is a constant ratio in favor of the greater incidence of diseases and other precipitating factors occurring at the incidence of stuttering among stutterers whose pedigrees show no ancestral stuttering than among stutterers whose pedigrees show ancestral stuttering. Many of the stutterers with pedigrees of ancestral stuttering show a history of no diseases or other precipitating factors coincident with the onset of speech and stuttering, as compared with the percentage of stutterers with pedigrees with no ancestral stuttering. The manner and character of the accidents, frights and diseases are more violent and more severe among those stutterers having pedigrees of no stuttering than among stutterers showing stuttering in their ancestry.

J. A. M. A.

PENIS ENVY AND URINARY CONTROL; PREGNANCY FANTASIES AND CONSTIPATION; EPISODES IN THE LIFE OF A LITTLE GIRL. WILLIAM G. BARRETT, Psychoanalyt. Quart. **8**:211, 1939.

The author describes a series of incidents in the life of a girl between the ages of 2½ and 4½ years, who showed attempts first to deny her lack of a penis and then to compensate for this lack by achieving an identification with her mother. Her first reaction to the conscious recognition of the fact that her brother possessed a penis was to deny its existence. She then began to evidence shyness about her own need to sit down to urinate. Several times she attempted to urinate while standing and was reluctant to accept the dismal failure. At about this time she began to have enuresis; her reaction was sometimes shame and sometimes a boisterous denial or blaming of her doll or the dog. She was unable to urinate in the presence of her brother or father. The mother dealt with this by taking the child to the toilet at intervals and by attempting to help her accept femininity by showing her that girls can enjoy certain pleasures that are denied boys, such as clothing, cosmetics and hairdressing, and that they might look forward to even more important compensations, such as the development of breasts and the birth of a baby. Enuresis rapidly ceased, and the following incident marked the end of the problem: She and her mother had just said "good-by" to her father on his departure to the office. As they walked up the stairs together, the girl reached for her mother's hand and said: "Daddy and brother are boys; mother and I are girls."

Shortly after her fourth birthday, a new difficulty arose. She became markedly constipated, and it was evident that she was deliberately retaining her stools. At this time the mother was pregnant, but to the best of her knowledge the girl did not know this. However, pregnancy fantasies seemed to be the cause of the symptoms, so the mother proceeded to tell her daughter that there was to be a new baby and offered to share it with her. The girl stared at her mother a few moments, smiled shyly and said: "Yes, I have one in my tummy." The mother explained to her she was too young to have a baby but that she could share the one in the mother's "tummy." They rehearsed together, in detail, how they would care for the baby. This resulted in the child having a large normal movement, with no further difficulties for three days. Then the child asked her mother if she had moved her bowels that day. When the mother said she had not, the child refused to have a movement, as though she were again afraid or unwilling to part with her baby. In order to counteract this, the mother made a point of talking more about the baby and going to the toilet in the child's presence. The little girl held out for three days, but when her confidence was restored the constipation disappeared.

PEARSON, Philadelphia.

THREE CASES OF PHENYLPYRUVIC OLIGOPHRENIA. R. N. BATES, J. Ment. Sc. **85**:273 (March) 1939.

Bates describes the physical characteristics in 3 cases of phenylpyruvic oligophrenia. The patients were boys, aged from 9 to 15 years, all of whom were imbeciles. They were "ash blondes"; in 1 case the hair had become lighter in the last two and one-half years. There was no pubic or axillary hair. The eyes were light blue. Examination of the fundi revealed pale optic nerve heads and a poorly developed choriocapillaris. The skin was very fair, with a marked tendency to dermographia and susceptibility to sunburn. All reflexes were hyperactive. There was cyanosis of both hands and feet. A brief trial with vitamin B_1 therapy in 2 of the cases was without effect on the excretion of phenylpyruvic acid.

KASANIN, San Francisco.

FACIAL EXPRESSION IN SCHIZOPHRENIC DRAWINGS. F. REITMANN, J. Ment. Sc. **85**:355 (March) 1939.

Six patients with schizophrenia, 4 with depressive psychoses and 3 with hysteria were tested for ability to recognize the various emotions depicted in twelve simple

line drawings and to reproduce certain of these drawings from memory. The results revealed no gross errors in describing the test pictures. The depressed patients emphasized the unhappy expressions; the schizophrenic patients made occasional bizarre associations, apparently autistically determined — they also offered no criticism of the drawings whereas the depressive and hysterical patient noted their poverty and stiffness of expression. The reproductive drawings of the schizophrenic subjects were more inaccurate than those of the other groups. They tended to "draw lines instead of pictures," reproducing the details, but in a pointless way with no regard for the total impression. The hysterical subjects, on the other hand, had little regard for reproduction of formal detail, but reproduced the expressions vividly. The drawings of the depressed patients were carefully done, but "have to be characterized mainly in negative terms."

KASANIN, San Francisco.

VASOMOTOR REACTIONS IN THE HYPNOTIC STATE. J. DOUPE, W. R. MILLER and W. K. KELLER, J. Neurol. & Psychiat. **2**:97 (April) 1939.

Doupe, Miller and Keller investigated the effects of hypnosis on the vasoconstrictor response produced by painful or thermal stimuli, in order to determine whether such a response was dependent on the "conscious" appreciation of the stimulus. The authors found that the hypnotic state itself did not alter the state of the peripheral circulation or the vasoconstrictor response. When a strong painful stimulus was applied to an area of hypnotically induced analgesia definite diminution in vasoconstriction resulted, whereas a moderate stimulus produced only slight reduction in the response as compared with that of a normal area. Grimacing and alterations in respiratory rhythm were also less marked from stimuli applied to the analgesic limb. Vasoconstriction followed mental activity and the suggestion of pain in both the normal and the hypnotic state, whereas suggestions of warmth or coolness produced no effect. The results of the experiments showed that the autonomic nervous system may be brought into activity by a noxious stimulus which is not consciously perceived and which does not set up an associated emotional state. These involuntary reactions are, however, further augmented by associated emotional states caused by appreciation of the pain. This explains the greater response with strong stimulation of the normal as compared with that of the analgesic side and the greater similarity of the responses on the two sides with light stimulation, in which case the stimuli are too slight to cause any mental anxiety. The reduction in the vasomotor response in the area of suggested analgesia is due to the fact that the suggestion prevents the perception of sensation by consciousness, while the residual response observed may be due to subconscious activities or may be in the nature of a spinal reflex. The state of the peripheral vessels cannot be altered by hypnotic suggestion, except in association with induced emotional states. The authors concluded, therefore, that vasoconstriction in response to painful stimuli is partly dependent on the feeling tone associated with an awareness of the stimulus.

MALAMUD, Ann Arbor, Mich.

POSTOPERATIVE DELIRIUM IN OPHTHALMOLOGIC PRACTICE. JEAN SÉDAN, Rev. d'oto-neuro-opht. **17**:168 (March) 1939.

Sédan discusses postoperative delirium following operations on the eye. Various explanations for this condition (senility, cortical deficiency, mental predisposition, toxemia) have been offered; probably more than one cause is operative. Study of 1 of 2 cases reported by Sédan seems to indicate conclusively that deprivation of vision was the sole explanation in this instance. The patient, aged 68 years, who was in perfect health, had become violent after an operation for cataract twenty-four years previously and had torn off the bandages. He injured the eye to such a degree that enucleation was required. After recovery he remained normal for twenty-four years, when a cataract developed in the other eye. As

his vision declined mental aberrations reappeared. He submitted to having the eye bandaged as a test and after a few hours became violent. The only recourse left was to operate and leave the eye unbandaged. The result was excellent, and the psychic state became entirely normal. Posey has reported a case of operation for cataract in a mentally ill person who recovered both vision and mental health afterward.

DENNIS, San Diego, Calif.

Diseases of the Brain

MANIFESTATIONS OF TRICHINIASIS IN THE CENTRAL NERVOUS SYSTEM. LORANCE B. EVERS, Arch. Int. Med. **63**:949 (May) 1939.

Evers reports a case of encephalitis resulting from trichiniasis. Fifteen cases of trichiniasis producing encephalitis, or encephalomyelitis with delirium, stupor or coma, and neurologic signs indicating diffuse involvement of the brain and of the spinal cord have been reported. Meningitis, neuroretinitis, optic neuritis, diplopia and dilatation of the pupils have been observed in patients suffering from the disease. A review of 110 cases of trichiniasis showed that there was absence of deep reflexes in 10 per cent. This sign has been attributed to neuritis, but in a recently reported case in which the deep reflexes were absent microscopic examination of the peripheral nerves failed to show evidence of degeneration.

Twenty-four cases have been reported in which larvae of Taenia spirilis have been isolated from the spinal fluid. Eleven of the patients recovered, while 4 died during the acute stage of the disease. The final outcome was not indicated in 9 cases. The spinal fluid pressure is occasionally increased, and lymphocytes, varying in number from 10 to 240 per cubic millimeter, are usually present. The other spinal fluid values are usually within normal limits. No definite relationship between the presence of larvae in the spinal fluid and the symptoms or signs of involvement of the central nervous system could be determined. Although the finding of larvae in the spinal fluid is not indicative of involvement of the central nervous system, this laboratory procedure may aid in the diagnosis of the disease in suspected cases.

BECK, Buffalo.

SPATIAL DISORIENTATION WITH HOMONYMOUS DEFECTS OF THE VISUAL FIELD. MARK KANZER and MORRIS B. BENDER, Arch. Ophth. **21**:439 (March) 1939.

Patients with homonymous hemianopia differ in the degree of cognizance of their defects. When the lesion is in the optic tract, the existence of partial blindness is constant and compensatory turning of the head and eyes develops. If this adjusted attitude is not established the patient stumbles against objects on his blind side, and in reading overlooks and miscalls words and letters. In some cases of lesions of the suprageniculate pathways the visual disturbances may be complicated by agnostic factors. The patient shows faulty comprehension of visual objects and consequently is unable to compensate automatically for his defects. Kleist distinguished between visual "object agnosia" and "spatial agnosia." In the former objects are not recognized, and in the latter, while the form is correctly perceived, difficulty in spatial orientation occurs. It is this spatial agnosia which is usually associated with homonymous hemianopia, though it may be found in the presence of normal fields. Various other observers have emphasized the abnormal distribution of attention which occurs in this condition, manifesting itself in such disorders as dyslexia, simultaneous agnosia and constructive apraxia.

Kanzer and Bender report in detail the findings in a patient with defects in the left homonymous field of vision and symptoms of tumor in the right cerebral hemisphere. Operation revealed an infiltrating spongioblastoma multiforme in the right occipital lobe. Examinations of the spatial orientation revealed a spontaneous tendency to direct visual attention to the right and to ignore objects to the left. There was general constriction of the field of attention, with displace-

ment of clearest vision to the right of the normal fixation point. These disturbances resulted in abnormal perception of visual configuration, with consequent concentration on details of a pattern rather than on survey of the total field. Objects at the fixation point were apt to be misinterpreted, a finding which is against any sharp distinction between object agnosia and spatial agnosia. Examination showed that disorientation in space resulted in dyslexia and in reactions such as characterize simultaneous agnosia and constructive apraxia.

Kanzer and Bender conclude: "As in the Korsakoff syndrome, a lively imagination and lack of critical attention obscure reality and make it possible for the patient to avoid a realization of his inadequacy. The mental picture and spatial disorientation appear to be functional disturbances which result from cortical destruction and complicate the adjustment to homonymous defects of the visual field."

SPAETH, Philadelphia.

TORTICOLLIS SPASTICA. OLAN R. HYNDMAN, Arch. Otolaryng. **29**:927 (June) 1939.

Hyndman reports 3 cases of spastic torticollis, in all of which the patient reacted strongly in Bárány tests. In 1 case relaxation of the spastic muscles was noted when the patient was reclining or when the head was tilted backward. In a case of spastic torticollis of seven years' duration, the spasmotic jerks of the head ceased completely when a cold caloric test was made on the left ear, and gradually returned after the induced nystagmus ceased. The spasmodic jerking of the head disappeared also when the right ear was irrigated with cold water. With the hot caloric stimulus the tendency for the spasmodic jerking to stop was much less striking than with the cold caloric stimulus. Severe stimulation of other parts of the body increased the torticollis. To eliminate the possibility of suggestion, the patient was informed that a test would be made as usual, but the water injected was at body temperature. The torticollis was not influenced. An acid ash diet with ammonia chloride was tried with benefit, after which it was decided to section the right vestibular nerve. The torticollis disappeared for ten days, but reappeared on the eleventh day. Three weeks after operation, a cold caloric stimulus was applied to the right ear to test the adequacy of the section of the vestibular nerve. The test had a mild and transitory influence on the torticollis. Auditory tests showed complete absence of audition on the side of the operation. During the ensuing four months the patient did not experience Ménière attacks of dizziness, but the torticollis was the same as before operation. Four months later the remainder of the eighth nerve was sectioned, without influence on the existing spontaneous cerebellar nystagmus. On the third postoperative day the torticollar twitches appeared. Two weeks later a cold caloric test on the right ear showed no reaction and had no influence on the torticollis. Five months after the second and four months after the first operation, cervical laminectomy with bilateral section of the first, second and third anterior roots and spinal accessory nerve was done. Fifteen days after discharge the spasms returned, but to a much less degree, indicating that, although the vestibular apparatus is involved in certain cases of spasmodic torticollis, destruction of the end organ in this case failed to abolish the torticollis permanently and that the locus operandi is central.

HUNTER, Philadelphia.

INTRACRANIAL HYPERTENSION OF UNKNOWN CAUSE: CEREBRAL EDEMA. ADOLPH L. SAHS and OLAN R. HYNDMAN, Arch. Surg. **38**:428 (March) 1939.

A syndrome variously referred to as "pseudotumor," "serous meningitis" and "otitic hydrocephalus," 5 cases of which are reported by Sahs and Hyndman, is probably due to cerebral edema, extracellular or intracellular or both. Consistently normal cerebrospinal fluid from the cytologic and the chemical standpoint excludes an inflammatory process of the cerebrum or meninges. Absence of the slightest evidence of ventricular dilatation at any time during the disease excludes the

possibility that decreased absorption or excessive production of cerebrospinal fluid is the cause of the increased tension. Likewise, this observation demonstrates that cerebral atrophy does not occur, and hence that the pathologic process is not destructive except for the atrophy which may follow prolonged papilledema. For the present, cerebral edema would be the most fitting diagnosis for this type of pseudotumor. Recovery is spontaneous, requiring months, and occurs even when no decompressive therapy is administered.

GRANT, Philadelphia.

SWELLING OF THE BRAIN IN CASES OF INJURY TO THE HEAD. PHILIP SHAPIRO and HARRY JACKSON, Arch. Surg. **38**:443 (March) 1939.

In autopsy material, the subarachnoid fluid in cases of trauma to the head was not increased but decreased. The ventricular fluid was increased in the presence of internal traumatic hydrocephalus. At death the brain in an injured head is not wet but dry; it is swollen but not edematous. Part of the enlargement of the brain in cases of trauma to the head is a result of ventricular distention. Part of the swelling of the brain after trauma to the head is accounted for by increased blood content from innumerable petechial hemorrhages. For the rest, the factor of unreleasable intracellular parenchymatous fluid can be assumed only by exclusion. The lines of therapeutic effort suggested by this study indicate that lumbar puncture and dehydration are indicated, but have probably been carried as far as possible. Ventricular drainage may be useful. Emphasis is placed on measures to reduce parenchymatous hemorrhage within the brain substance.

GRANT, Philadelphia.

DIAGNOSTIC STUDY OF PSEUDOTUMORAL ENCEPHALITIS. H. ROGER, M. ARNAUD and J. L. PAILLAS, Presse méd. **47**:485 (April 1) 1939.

Roger and his associates point out that the term "pseudotumor" was first applied by Nonne in 1904 to those conditions the clinical aspects of which simulated a cerebral tumor but in which the favorable development or the postmortem observations contradicted the diagnosis of tumor. Nonne's description included different meningeal, arachnoid and parenchymatous lesions. In this report the authors present a diagnostic study of the inflammatory parenchymatous lesions. They first discuss the progressive forms of encephalitis, which, although rarer than the regressive forms, are better known. Among the forms of progressive encephalitis the leukoencephalitides are the most important; they may appear in the form of Heubner-Schilder's disease and of Balo's disease. The regressive forms of pseudotumoral encephalitis the authors divide into two groups. In the first group they combine the localized or circumscribed forms with focal symptoms, which are especially likely to simulate cerebral tumor. They describe the clinical histories of several cases of this type. The second group includes the more diffuse forms, in which the symptoms vary greatly. In a review of the clinical elements which might be of value in the differentiation of neoplasm and encephalitis, the authors show that such signs are inconstant and of doubtful value. They say that the syndrome of intracranial hypertension with papillary stasis contraindicates lumbar puncture; examination of the ventricular fluid, which they performed in the course of the ventriculographic procedure, always gave normal results. Ophthalmoscopic examination reveals papillary edema; the diagnosis of pseudotumoral encephalitis can be based on this sign. The papillary edema is accompanied by considerable lowering of visual acuity and abnormal modification of the visual field, but the most noteworthy ophthalmologic aspect is the absence of retinal arterial hypertension. Ventriculographic examination gives the most reliable information for the detection of pseudotumoral encephalitis. Moreover, it may even exert a favorable therapeutic influence. The prognosis of pseudotumoral encephalitis varies. Leukoencephalitis has a fatal outcome, but the regressive forms usually end favorably. The treatment consists in the early, intense and prolonged administration of diffusible anti-infectious medicaments.

Moreover, the endocranial insufflation of air may exert a powerful therapeutic effect. Craniotomy, besides being of exploratory value, is effective as a decompressive measure.

J. A. M. A.

NERVOUS COMPLICATIONS OF NICOLAS-FAVRE DISEASE (VENEREAL LYMPHOGRANULOMA). LÉVY-VALENSI and S. DE SÈZE, Presse méd. **47**:593 (April 19) 1939.

Lévy-Valensi and de Sèze show that until now little attention has been given to the nervous manifestations in the course of venereal lymphogranuloma. They think that these nervous complications are less exceptional than is generally believed. Their attention was called to this problem by the appearance of acute myelitis in the course of venereal lymphogranuloma in a case in which the examination of the cerebrospinal fluid disclosed the presence of Proteus vulgaris. After considering the two possibilities that are suggested by this case, namely, that the meningomyelitis was caused by P. vulgaris or that it was a true nervous complication of venereal lymphogranuloma, they state that in 1931 Nicolas observed in the course of venereal lymphogranuloma persistent headaches, fever and rigidity of the neck, symptoms which are usually attributed to meningeal processes; von Haam and d'Aunoy observed headaches in the acute stage of the disease; sciatic and crural neuralgias were observed by several authors; intense, persistent headaches and fever were observed by Prats in 52 of 100 cases of venereal lymphogranuloma. Grave nervous symptoms in the form of flaccid paralysis, epileptiform crises and grave (even fatal) meningoencephalitis were observed by Marinesco and several others. The authors further cite experimental and biologic studies on the neutrotropic power of the virus of venereal lymphogranuloma, pointing out that acute leptomeningitis and meningoencephalitis have been produced by the virus of venereal lymphogranuloma in certain species of monkeys. In mice the virus has been known to produce, after several passages, a fatal disorder characterized by motor disturbances. In studies on the cerebrospinal fluid of patients with venereal lymphogranuloma, some investigators failed to detect pathologic changes, whereas others observed increased tension, lymphocytosis and positive Pandy and Nonne-Apelt reactions. In investigating the virulence of the cerebrospinal fluid of 8 patients with venereal lymphogranuloma, von Haam and d'Aunoy succeeded in 2 cases in infecting mice by intracerebral inoculation and in carrying the infection through several animal passages. Thus the notion of a clinical neurotropism of the virus of venereal lymphogranuloma, far from having been contradicted by animal experimentation and biologic analysis, has been supported by some of the observations in the course of these studies.

J. A. M. A.

MALIGNANT EXACERBATION OF MULTIPLE SCLEROSIS. A. JUBA, Arch. f. Psychiat. **109**:727 (April 15) 1939.

Juba thinks that for clarification of the relations between multiple sclerosis and encephalomyelitis disseminata, as far as this is morphologically possible, the cases of multiple sclerosis are especially suited in which death resulted from a peracute exacerbation. He describes 3 microscopically verified cases of multiple sclerosis in which, after a chronic or intermittent course, a peracute exacerbation set in. Death followed in the first case after thirteen days, in the second after seventeen days and in the third after five days. In the first case, one of hemiplegia, anatomic examination disclosed in the medullary substance of the hemispheres many perivascular, encephalomyelitic foci with indefinite outlines. Formation of glia could be observed in a young focus of the wall of the lateral ventricle. In the second case, one of tetraplegia with spastic and bulbar symptoms, a sharply defined, new destruction of the medullary substance was demonstrable in the upper cervical section and in the closed medulla oblongata. In the third case the spastic paraparesis was suddenly transformed into flaccid paralysis; in the anterior horns of the spinal cord sharply defined, symmetric foci were observed, the central portion of which had broken down. As common characteristics of the acute process the

author detected the formation of glial foci around the vessels and about the fluid space, with special affinity for the white substance; at any rate, the ganglion cells remained relatively free. As far as the morphologic aspects are concerned, there are doubtless close relations to encephalomyelitis disseminata. Especially characteristic is the rapid growth of the foci, so that the process is not restricted to the juxtavascular region but penetrates deep into the parenchyma; then there are the sharp demarcation and the severe inflammation, which together give a characteristic aspect to the acute phase of multiple sclerosis. If these characteristics are accepted as criteria of the acute phase of multiple sclerosis, and if the morphologic aspects of the cases of encephalomyelitis disseminata are considered, it seems probable that there is a form which belongs to the group of multiple sclerosis and is an especially malignant type of the disease. On the other hand, there are cases in which the disease has no connection with multiple sclerosis and in which, as regards the structure, it closely resembles the parainfectious encephalomyelitides. As to the pathogenesis, the author says that he adheres to the theory of the inflammatory character of multiple sclerosis. He admits that the foci usually form around the vessels, but says that they also form around the fluid spaces. He does not share Putnam's theory of the causal significance of circulatory disturbances and especially the formation of thrombin in the small vessels; Juba neither detected thrombi nor observed that the process was restricted to the perivascular region.

J. A. M. A.

TRAUMATIC EPILEPSY. E. KATZENSTEIN-SUTRO, Schweiz. Arch. f. Neurol. u. Psychiat. **41**:458, 1938.

The intellectual defects and changes in character which may result from cerebral trauma are noted almost without exception in the histories of patients suffering from traumatic epilepsy. Mental changes may, under certain conditions, presage the later development of convulsive seizures.

Of 7 patients suffering from traumatic epilepsy, whose cases are reported by the author, the first, a girl aged 4 years, showed changes in personality immediately after an apparently trivial injury and became subject to petit mal five months later. Convulsive attacks limited to the right side of the body appeared a year after the accident, and neurologic examination subsequently disclosed hemiparesis on this side. A thickened dura overlying the left parietal lobe was removed surgically. At the other extreme was the case of a man who was seriously injured in his thirtieth year; he became addicted to alcohol and was declared mentally incompetent, but did not have convulsive seizures until twenty-one years after the accident. He died in status epilepticus at the age of 80; postmortem examination revealed marked atrophy of the left frontal lobe, which on its inferior surface presented a gross defect communicating with the lateral ventricle. Another patient, a girl aged 19 years, had sustained an injury to the head, of moderate severity, in her fourth year and became subject two years later to minor seizures, which ceased after two years, only to recur when the patient was 16 years old. Operation at the site of a previous fracture of the skull revealed thickening of the dura and edema of the leptomeninges; the altered dura was removed, and the attacks ceased. In 3 cases one of the lateral ventricles was found on encephalographic study to be dilated and drawn toward the surface of the skull. Excision of rather extensive scars involving the pia and cerebral substance was followed by cessation of jacksonian seizures in 2 of these cases, but the third patient was drowned three months after operation, presumably during a generalized convulsion. In the last case, fat, which had been used to close the cerebral defect, was found on postmortem study to have induced a rather marked inflammatory reaction; much of it was contained within a number of cysts, in the walls of which were numerous foreign body giant cells containing fat droplets.

Death occurred in 1 case while preliminary studies were in progress. The patient, a man aged 21, had had a single seizure limited to the left side of the body shortly after sustaining an injury to the head in his fifth year. Fifteen years

later, on the day after he had worked with his head hyperextended, he had a generalized convulsion, which was followed by six more in the ensuing fourteen months. Autopsy disclosed a multilocular cyst in the atrophied right frontal lobe, communicating with the lateral ventricle. The overlying dura and leptomeninges were fused in a dense scar, from which strands of connective tissue extended into the cerebral substance.

Histologic examination of tissue removed either at operation or at autopsy in the cases reported indicated that both glial and mesodermal elements had taken part in the formation of the cerebral scars. Lymphocytic infiltrations were observed in and about the scar tissue in 3 cases, despite the absence of bony defects. Though subscribing to the views of Foerster and Penfield relative to the importance of traction exerted by contracting scars, the author suggests that "symptomatic inflammatory processes" may also play a part in the causation of epileptiform seizures. In some of the cases studied considerable amounts of hemosiderin were observed in the altered tissues.

DANIELS, Denver.

Peripheral and Cranial Nerves

NEUROFIBROMA OF THE FACIAL NERVE IN THE FACIAL CANAL. HENRY L. WILLIAMS and PETER N. PASTORE, Arch. Otolaryng. **29**:977 (June) 1939.

Williams and Pastore report the case of a patient who had had left facial paralysis for four years, accompanied by soreness in the left mastoid region, deafness and tinnitus. There was complete nerve deafness on the left. Roentgenograms revealed destruction of the mastoid bone. General physical and neurologic tests gave normal results. A radical left mastoidectomy was done, and yellowish, soft material was observed at the cortex and just above the posterior wall of the external canal. The labyrinth was invaded. The tumor was a neurofibroma. This is the first case of neurofibroma of the facial nerve involving the mastoid bone to be reported.

HUNTER, Philadelphia.

VITAMIN B_1 IN ALCOHOLIC POLYNEURITIS. A. J. MCGEE, Illinois M. J. **75**:470 (May) 1939.

McGee states that between a group of 25 patients with alcoholic polyneuritis treated by subcutaneous hypodermic injection of vitamin B_1 (thiamin chloride) and a control group of 23 patients receiving only the vitamin B_1 contained in the diet there was practically no difference in the time required for complete alleviation of symptoms. The severity of the symptoms and the time required for recovery seem to be directly proportional to the duration of the neuritis. Of the patients with severe neuritis, subjective relief was obtained in the group treated with vitamin B_1 in an average of ten and four-tenths days and in the control group in eighteen days. In the treated group of patients with the moderately severe form complete relief of all symptoms was obtained in an average of six and one-tenth days and in the control group in six and a half days. In the treated group with the mild form complete relief occurred in an average of four and three-tenths days and in the control group in four and a half days. There were no patients in either group who failed to show improvement

J. A. M. A.

THE EXPERIMENTAL POLYNEURITIDES. J. DE AJURIAGUERRA, Rev. neurol. **70**: 433, 1938.

The mechanism of the polyneuritides has been the subject of divergent opinions. Erb, Pierre Marie and Babinski expressed the belief that the nerve lesions were secondary to those of the central nervous system. Babinski admitted leprous neuritis as the only exception. Joffroy, Pierret, Pitres and Vaillard, Dejerine and Mme. Dejerine and Renault asserted that the nerves were susceptible to local

injury, independent of a previous lesion of the ganglion cells. Villaverde interpreted concomitant lesions of the ventral horns and of the nerves as simultaneous, but usually parallel and not dependent one on the other. Experiments on animals have not entirely solved this problem. Lhermitte, Kulikowsky and Trelles observed destructive lesions in the fourth and fifth layers of the cerebral cortex, the Purkinje cells and the dentate nucleus of the cerebellum in rabbits given injections of lead diethylphosphate. The spinal gray matter was far less involved. The spinal white matter showed swelling and varicosity of the axons. The ganglia and the nerves were intact, even in cases in which the spinal radicular cells were severely involved. Injections of bee venom in rabbits resulted in extensive lesions of the central ganglion cells but not in lesions of the nerves, while injection into the sheath of the sciatic nerve produced severe local degeneration. Diphtheritic paralysis was produced experimentally in the rabbit in most instances. The guinea pig showed paralysis comparable with the human type. In this species Lhermitte observed degeneration of the nerves and skeletal muscles while the central nervous system was intact. Guinea pigs were treated with tetanus toxin incompletely transformed into antitoxin. Tonic spasm, spreading to the whole body and ending in generalized rigidity, but with no paroxysms such as those seen in man, resulted. The spinal radicular cells showed either swelling of the cytoplasm, with chromatolysis and vacuolation, cytolysis, karyolysis and cell shadows, or retraction and hyperchromatophilia. The cytolytic figures were surrounded by numerous microglial satellites. The oligodendroglia of the gray matter was diffusely proliferated. The spinal ganglion cells showed similar lesions. The sciatic nerve showed extremely variable grades of degeneration, often not proportional to the medullary lesions. Rabbits were fed absinth. One group received a diet limited to bread; the others were given varied food. All were severely paralyzed and dyspneic by the fortieth day. The spinal radicular cells, the Purkinje cells and the cerebral cortex, particularly the Betz cells and the fifth layer generally, showed extensive chromatolysis, karyolysis and vacuolation. The nerves were intact. One rabbit was treated with absinth and at the same time received injections of thiamin. Paralysis developed after three months. The central lesions were far less severe than those in the other animals, but the nerves showed scattered beading and varicosity of the axons. Polyneuritis may exist independently of lesions of the central nervous system, as in experimental diphtheritic paralysis. In other instances the nerves and the centers may be simultaneously injured.

LIBER, New York.

FURTHER CASES OF SPONTANEOUS POLIOMYELITIS IN DOMESTIC ANIMALS (HOGS). E. FRAUCHIGER and W. MESSERLI, Schweiz. med. Wchnschr. **69**:74 (Jan. 28) 1939.

Frauchiger and Messerli say that since acute anterior poliomyelitis has been observed in cattle they have given special attention to paralytic symptoms in domestic animals. In this report they describe observations on 2 hogs which presented symptoms that greatly resembled those of acute anterior poliomyelitis. On the basis of these symptoms the disorder was diagnosed as probable poliomyelitis. Both animals were killed, and microscopic examination of the spinal cords revealed in both histologic appearances resembling those of acute anterior poliomyelitis in human subjects. Material from the spinal cords of these animals was introduced into 2 other hogs and 1 steer. Because of an inadequate technic, nothing could be learned from the inoculation test on the hogs, but in the case of the steer, in which a formerly devised technic was employed for the inoculation, fever developed, the curve of which showed the dromedary type. Other symptoms included signs of fatigue, stiffness of the neck and an ataxic gait. From the seventh day after the inoculation the symptoms commenced to subside, and a few days later the animal seemed normal again. The animal was killed fourteen days after the inoculation. The histologic appearances of the central nervous system were those of lymphocytic meningoencephalomyelitis rather than those charac-

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teristic of poliomyelitis, but it must be remembered that the animal was not killed during the acute stage, when signs more typical of poliomyelitis might have been detected. However, since Spielmeyer's investigations demonstrated that similar histologic appearances do not necessarily indicate the same disease or causal agent, the authors do not definitely conclude that the described paralytic symptoms in hogs are identical with those in human poliomyelitis, but they believe that this may be the case. They think that the detection of further cases of poliomyelitis in animals and the transmission of the disease from animal to animal and from man to animal will provide more certainty.

J. A. M. A.

POLYNEURITIS CEREBRALIS IDIOPATHICA. IVO GLAVAN, Ztschr. f. d. ges. Neurol. u. Psychiat. **164**:692 (Feb.) 1939.

Glavan reports a case of what he believes to be a virus infection of some of the cranial nerves without involvement of the brain, spinal cord or peripheral nerves in a man aged 33, without evidence of syphilis. The onset was sudden, with fever. There was increase of protein and of lymphocytes in the spinal fluid. Soon after the onset of malaise and fever, the patient complained of neuralgic pains in the area of distribution of the trigeminal nerve, especially the third division. On the third day the left side of the face was involved, and three days later peripheral paralysis of the right side of the face appeared. Tinnitus on both sides was present for a few days. There was no diminution of hearing. The corneal reflex was diminished on the right side and absent on the left. There was diminution of sensation on the left side of the face. Facial diplegia was present. Both the fifth and the seventh, and probably the eighth, cranial nerve were involved in this case. In the other case reported by Glavan there was symmetric involvement of eight pairs of cranial nerves, the third, fourth, fifth, sixth, seventh, eighth, ninth and tenth (*Arch. f. Psychiat.* **108**:668, 1938).

SAVITSKY, New York.

Vegetative and Endocrine Systems

THE DAILY EXCRETION OF URINARY ANDROGENS IN NORMAL CHILDREN. IRA T. NATHANSON, L. E. TOWNE and J. C. AUB, Endocrinology **24**:335 (March) 1939.

The authors report the urinary assay for androgen in 4 boys and 6 girls ranging in age from 7 years and 7 months to 12 years and 5 months. The results were obtained from assays on complete twenty-four hour specimens of urine collected every third or fourth day for periods varying from two to five weeks. The results indicate that there is a definite variation in excretion of androgen from day to day, but that the change is not physiologically significant. Young children show less variation than the preadolescent or adolescent groups. There is no evidence of a cyclic excretion, but there is a general level for any age group when the factors of increasing chronologic age and of physical maturity are taken into consideration. Excretion in boys is slightly higher than in girls of the same age and size.

PALMER, Philadelphia.

AGE AND SEX DIFFERENCES IN HORMONE CONTENT OF THE RABBIT HYPOPHYSIS. J. A. SAXTON JR. and H. S. N. GREENE, Endocrinology **24**:494 (April) 1939.

Saxton and Greene studied the effects of transplantation into immature female guinea pigs of the pituitary gland from freshly killed rabbits. The pituitary glands were analyzed by daily implantation of one fourth of the gland of adult rabbits and of one-half to two glands of young rabbits, depending on their size. The posterior lobe was not removed before implantation. The subcutaneous implants were made daily for four days, and the immature female guinea pigs were killed for examination on the fifth day. At autopsy both ovaries and the left adrenal gland of each

guinea pig were weighed, and the gross appearance of the thyroid, uterus and vagina was noted. It was found that the pituitary gland from the male produced greater follicular stimulation and luteinizing effect than did that of the female, as well as greater stimulation of the adrenal cortex. The thyrotropic effects were approximately equal. Pituitary glands from immature, 10 day old rabbits caused stimulation of the thyroid and adrenal glands but no gonadotropic effects. Those from rabbits from 15 to 21 days of age produced follicular stimulation. Glands from rabbits 28 days of age and older produced both follicular stimulation and luteinization, though of a moderate degree. The thyrotropic effects of pituitary tissue from immature rabbits were greater than those of comparable amounts from mature rabbits. Glands from old female rabbits produced about the same degree of follicular stimulation and luteinization as those from young mature females. There were less stimulation of the thyroid and, generally, greater stimulation of the adrenal cortex. The results of implanting glands from older, mature rabbits indicate that there is no appreciable change in the amounts of the gonadotropic hormone with increasing age and sexual maturity. Similarly, human hypophyses showed no change in this respect. There was, however, in the case of rabbits a tendency for the thyrotropic hormone content to diminish and for the adrenal-stimulating factor to increase with age. PALMER, Philadelphia.

ELECTROCARDIOGRAPHIC CHANGES DURING HYPOGLYCEMIA AND ANOXEMIA. H. E. HIMWICH, S. J. MARTIN, F. A. D. ALEXANDER and J. F. FAZEKAS, Endocrinology **24**:536 (April) 1939.

The authors report electrocardiographic changes observed during hypoglycemia and anoxemia in 5 dogs. Injections of protamine zinc insulin were given the night before the experiment and standard insulin on the following day in doses adequate to produce coma and marked slowing of the heart rate. Anoxemia was induced in 9 dogs by inhalation of nitrogen monoxide or nitrogen. Intravenous injections of metrazol were also given to 3 dogs, since it had been proved previously that convulsions induced anoxemia. These agents were also administered to 4 hypoglycemic dogs; in all the cases anoxemia was continued until cardiac changes were observed, after which oxygen was administered. Sixteen experiments were performed in all, in 9 of which electrocardiagraphic disturbances during hypoglycemia and anoxemia were observed before and after bilateral vagotomy. In 2 dogs complete stellate ganglionectomy and splanchnectomy were performed. Similar studies were carried out in 11 cases with intraperitoneal injections of sodium pentobarbital to simulate the treatment of schizophrenia; in 5 instances no medication was given. Electrocardiographic studies showed that in hypoglycemia and anoxemia an initial transitory sympathetic influence was followed by parasympathetic predominance. This increased activity of the autonomic nervous system was associated with depressed metabolism of the brain, as indicated by diminished cerebral utilization of oxygen. The authors conclude that with depression of cerebral metabolism the predominant and ultimate effect on the autonomic nervous system is a release of parasympathetic influence. Hypoglycemia and anoxemia exert similar effects on the autonomic nervous system. Nitrogen, nitrogen monoxide and metrazol all reduced the oxygen available to the entire organism, including the brain. Insulin, on the other hand, produces its effect by depriving the brain of carbohydrate. With depression of the cortex release of subcortical function follows, expressed by increased activity of the autonomic nervous system through centers situated in the hypothalamus and medulla. PALMER, Philadelphia.

A CASE OF PITUITARY DWARFISM TREATED WITH ANTUITRIN-G [ANTERIOR PITUITARY EXTRACT]. J. A. BUCHANAN and H. A. BALLWEG, Endocrinology **24**:565 (April) 1939.

Buchanan and Ballweg report the results of therapy with antuitrin-G (a pituitary extract containing the growth hormone) in a girl aged 18 suffering from

dwarfism due to a tumor of the pituitary, with hypofunction in the production of growth and gonadotropic hormones. When first seen in January 1937, the patient weighed 65 pounds (29.5 Kg.) and was 51⅝ inches (131 cm.) tall. She was first given 1 cc. of antuitrin-G daily for two days, and then 2 cc. daily for twelve days, after which the presenting symptoms (nausea, vomiting and headache) became less severe. Treatment with antuitrin-G was continued for eleven months, 2 cc. being given for a time every second day and then every third day. The patient gained 17¾ pounds (8.1 Kg.) and increased 1¼ inches (3.18 cm.) in height. There followed also the appearance of axillary hair and the establishment of catamenia with enlargement of the breasts. Necropsy revealed a tumor of an undetermined type in the region of the pituitary gland, involving the floor of the third ventricle and the pituitary gland.

PALMER, Philadelphia.

HIBERNATION AND THE ENDOCRINES. M. A. FOSTER, R. C. FOSTER and R. K. MEYER, Endocrinology **24**:603 (May) 1939.

The authors made a study of the thirteen line ground squirrel to determine the endocrine relationships involved in hibernation. The animals were taken from their natural environment during the summer and fall seasons and allowed to remain in the laboratory until they were ready for use. In preparation for hibernation they were placed in cages containing nesting material, dry food and no water. After the animals were weighed they were placed in a cold room, with a temperature of 36 F. Studies were made of normal animals during the different seasons, both with and without water. The effects of glandular hyperactivity, induced by the administration of extracts, on the tendency to hibernate during the nonbreeding season were observed. By contrast, the extirpation of these glands was carried out during the breeding season, when the animals were resistant to cold and could not be induced to hibernate. A series of sexually active animals, both male and female, were hypophysectomized. Atrophy of the gonads and other secondary endocrine organs resulted, but the ability to resist cold was retained for from seven to ten days. After this time, however, there was marked sensitivity to cold, and hibernating states developed more quickly than under normal conditions. Hibernation lasted only three days, and unless the animals were removed from the cold, death ensued. Owing to the depletion of the glycogen reserve in hypophysectomized animals, it is probable that hypoglycemia was a factor in their death. Attempts to convert sexually inactive (poikilothermic) animals into homeothermic animals by means of pituitary extract were successful. Extirpation of the thyroid gland failed to alter the homeothermic state, suggesting a direct metabolic function of the pituitary gland. This was established by showing that pituitary extracts were capable of inducing a "cold resistant state" in thyroidectomized animals during the nonbreeding season, when they would normally hibernate readily. Substitution therapy by thyroid or other means of producing hypermetabolism converted poikilothermic into homeothermic animals only for the duration of the metabolic stimulation. Removal of the thyroid, adrenal glands or gonads produced no significant effects, but substitution therapy during the nonbreeding (poikilothermic) season with pituitary preparations resulted in transient homeothermism. Similar results were obtained with thyroid preparations, but an extract containing the gonadotropic principle of the pituitary gland, adrenal cortex extract and estrogen were without effect. These findings suggest inactivity of the pituitary gland as the primary factor responsible for the phenomenon of hibernation.

PALMER, Philadelphia.

MIGRAINE: PITUITARY STUDY. R. O. HALLORAN, West Virginia M. J. **35**:233 (May) 1939.

Halloran proposes that migraine is due to swelling of the pituitary gland, which creates compression of the cavernous sinuses, resulting in congestion of the

whole venous system of the skull. Pressure on the pain papilla within the walls of the dural sinuses creates the headaches. The various components of migraine are thought to be pressure phenomena having their origin in the nerve structures in and about the cavernous sinuses and the sella turcica. It is further proposed that ergotamine tartrate (gynergen) decreases the vascular bed of the skull and brain, which in turn relieves the congestion and headache. The depression following migraine is thought to be due to accumulation of metabolites in the sensorium. Thus many mental states may be due to anoxemia of the brain. Further studies are indicated in the use of ergotamine tartrate and oxygen in the treatment of mental ills, acute alcoholism and delirium tremens. A close analogy of migraine, epilepsy and eclampsia is suggested. The periodic attacks of migraine are in keeping with the periodic fluctuations of the pituitary. There are many cases of migraine due to allergy. The author believes that explanation of this may lie in the fact that the anterior lobe of the pituitary is derived from the pouch of Rathke, from which the nasal mucosa is derived. The latter is allergic. Hence it is not unlikely that the anterior lobe is an allergic shock tissue and responds to allergens by swelling.

J. A. M. A.

SYMPTOMS OF HYPOPHYSIAL WEAKNESS IN CASES OF SUBNORMAL WEIGHT. W. KERPPOLA, Acta med. Scandinav. **99**:287, 1939.

In remarks about Simmonds' disease, Kerppola says that whereas the literature contains many reports of cases of the completely developed form of this disease, the milder forms have received little attention. The author decided to investigate whether symptoms of hypophysial weakness can be detected in emaciated persons in whom the subnormal weight cannot be explained by other diseases. He reports studies on 40 such patients, whose ages varied between 16 and 45 years. In the course of these studies it was found that the patients had many symptoms that are characteristic of hypophysial weakness. About half of the patients had a low sugar tolerance curve, relative lymphocytosis and low hydrochloric acid values. In approximately one third of the patients a relatively small sella turcica, mild anemia and granulocytopenia were observed. Menstrual disturbances, low stature and low metabolic rates were found in a small number of cases. A complex of symptoms characteristic of hypophysial weakness was present only in a limited form and only in a small number of cases. The material examined included conditions ranging from complete normality through all transitional forms to the symptoms of hypophysial weakness.

J. A. M. A.

Cerebrospinal Fluid

NEUTROPHILIC LEUKOCYTOSIS IN SPINAL FLUID ASSOCIATED WITH CEREBRAL VASCULAR ACCIDENTS. STUART R. TOWNSEND, ROBERT L. CRAIG and ALBERT L. BRAUNSTEIN, Arch. Int. Med. **63**:848 (May) 1939.

Six cases are reported in which softening or hemorrhage within the brain was associated with an increase of polymorphonuclear neutrophilic leukocytes in the spinal fluid. There may be an abundant response of polymorphonuclear leukocytes, giving a cloudy spinal fluid suggestive of meningitis, or an increase in cells which may be detected only on examination. The leukocytosis usually begins within several hours after the infarction and gradually disappears during a period of five to six days. In the cases reported in this paper, the number of cells varied between 50 and 3,000 per cubic millimeter, although cases have been described in which there were as many as 10,000 cells. In patients in whom the leukocytosis is great clinical evidence of meningeal irritation may occur. In no reported case has any definite clinical or postmortem evidence of an infectious process been shown. The most logical explanation of this meningeal reaction is a leukocytic response around the focus of softening or hemorrhage.

BECK, Buffalo.

CEREBROSPINAL FLUID IN OPTIC NEURITIS, "TOXIC AMBLYOPIA" AND TUMORS PRODUCING CENTRAL SCOTOMAS. A. L. WATKINS, New England J. Med. **220**: 227 (Feb. 9) 1939.

From examination of 120 patients who came to the hospital because of failing vision, 40 of whom had a disorder diagnosed as acute retrobulbar neuritis, Watkins concludes that the cerebrospinal fluid in acute conditions is normal, except in cases of multiple sclerosis. In cases of the acute type, which form from 25 to 50 per cent of the group, the colloidal gold curve may show a strong first zone reaction. In 39 cases of chronic retrobulbar optic neuritis the onset of the visual disturbance was slow and gradually progressive over a period of months, rather than weeks. The average age of 39 was somewhat higher than that (of 33) in the cases of acute neuritis, with 62 per cent of the patients more than 40 years of age. Both eyes were affected slightly more frequently (in 54 per cent) than one alone, and the eyeballs were tender and painful in only 22 per cent. Pallor of the optic disks was usually observed (in 72 per cent), but they were hyperemic in 21 per cent, and normal in 7 per cent. The characteristic field presented a central scotoma, and the visual impairment showed progression to nearly complete blindness. Lumbar punctures revealed no abnormality in the initial pressure, cellular content, total amount of protein or colloidal gold curve. The cause was unknown in 85 per cent of the cases and proved to be multiple sclerosis in 15 per cent. The average age in the 30 cases of "toxic amblyopia" was 52. The course was one of slow progressive loss of vision in the two eyes, although not necessarily in equal degrees. The eyeballs were in no case tender, and the optic disks were either normal or slightly pale. The diagnosis was made from visual field examinations, the characteristic field showing a cecocentral scotoma, although in some cases it was made from a history of overindulgence in alcohol and tobacco and the presence of a central scotoma similar to that in retrobulbar neuritis. Forty per cent of the patients improved after reducing or stopping the use of tobacco or alcohol. Cerebrospinal fluid examinations showed initial pressures which were usually normal. The total protein averaged 33 mg. per hundred cubic centimeters, being distinctly abnormal in only 2 cases. The colloidal gold curve was normal in all cases. Five patients showed diminution of vision, papillitis and a constricted field of vision. These 5 patients were between 4 and 44 years of age. There was tenderness of the eyeball in only 1 case. There were slight choking of the optic disks and peripheral constriction of the visual fields; in some cases there was only unilateral involvement. Lumbar punctures showed normal initial pressures. In all cases the disease was of fairly rapid onset, and normal vision was regained. Pansinusitis occurred coincidentally in 2 cases and hay fever in another. One patient had definite lead intoxication, which seemed of etiologic significance. Of 6 other patients with optic neuritis, 3 had transverse lesions of the spinal cord and retrobulbar neuritis which was thought to be on an unclassified infectious basis, but fitted into the clinical syndrome of optic neuromyelitis. The other 3 presented blindness with central scotomas and multiple peripheral neuritis. Necropsy in 1 of these cases revealed extensive periarteritis. In the 3 cases of optic neuromyelitis and the 2 of multiple peripheral neuritis with optic neuritis there was definite abnormality of the cerebrospinal fluid. In the case of periarteritis the fluid was normal. In an additional 22 cases of tumor associated with failing vision, the author found that the cerebrospinal fluid pressure, cellular content and colloidal gold curve might all frequently be within normal limits but that the total protein was usually increased from two to five times the normal when there was present a central scotoma from pressure of a tumor or aneurysm on the optic nerves or chiasm. J. A. M. A.

CEREBROSPINAL FLUID IN SYPHILIS OF THE CENTRAL NERVOUS SYSTEM: A PHYSICOCHEMICAL STUDY. M. SPIEGEL-ADOLF, Confinia neurol. **2**:1, 1939.

Since combined conductivity and interferometry studies have given valuable information in other conditions, Spiegel-Adolf carried out similar studies in cases

of syphilis. She found that the nonelectrolyte-electrolyte ratio was markedly higher (0.35) in patients with syphilis than in nonsyphilitic patients (0.31). The highest values were found in cases of dementia paralytica (0.41), while in those of tabes dorsalis the average was lower (0.34). For some intensively treated patients, as well as for 3 patients with "burned out" tabes, these values were the principal laboratory findings. In several cases a decrease in the ratio accompanied the improvement which followed therapy. DE JONG, Ann Arbor, Mich.

Treatment, Neurosurgery

USE OF FLUIDS AND LUMBAR PUNCTURE IN TREATMENT OF DELIRIUM TREMENS. J. M. THOMAS, E. V. SEMRAD and R. S. SCHWAB, Ann. Int. Med. **12**:2006 (June) 1939.

Thomas and his colleagues compared 20 patients with delirium tremens who had a lumbar puncture and were restricted in intake of fluids with 20 who did not have a lumbar puncture and were given large quantities of fluids. All 40 patients recovered from the delirium within one to three days after admission. However, the patients in the second group showed less tremor and fewer signs of exhaustion after the acute features of their mental disorder subsided than the patients who were restricted in their fluid intake and had lumbar puncture. Several patients of the latter group, who could not be kept in bed the usual length of time after the lumbar puncture, suffered from headache. The authors conclude from a careful scrutiny of the results of the two technics that lumbar puncture is of great diagnostic significance in delirium tremens, but that it is not an important factor in its treatment and that in the absence of intracranial complications (which are known to initiate an increase of cerebrospinal pressure) it is wiser to give patients with delirium tremens large quantities of fluids than to restrict this intake.

J. A. M. A.

TREATMENT OF DEAFNESS AND CONTIGUOUS NERVOUS DISORDERS WITH PROSTIGMINE. T. CARROLL DAVIS and JOHN C. ROMMEL, Arch. Otolaryng. **29**:751 (May) 1939.

Davis and Rommel found that intramuscular injections of prostigmine were beneficial in some types of deafness. Prostigmine methylsulfate, 1:2,000, was used in doses of 1 cc. every three to ten days. The authors believe that stimulation of the tensor tympani and the stapedius muscles accounted for the improvement in hearing. Two patients with hypertrophy of the thyroid showed toxic symptoms when the drug was administered. No other patient showed any untoward effects, although in some patients the drug was given for five months without interruption. Twenty-eight patients with acute blocking of the eustachian tube with tinnitus aurium, in most of whom the condition was accompanied by marked deafness, were given the drug. Few required more than five injections. Twenty-nine patients with chronic deafness and tinnitus aurium and 1 with trigeminal neuraligia were treated; many of them improved. HUNTER, Philadelphia.

THE TREATMENT OF FEMALE MENOPAUSE WITH MALE SEX HORMONE [ANDROGEN]. L. KURZROK, C. H. BIRNBERG and S. LIVINGSTON, Endocrinology **24**:347 (March) 1939.

The authors report 21 cases of the menopause in women ranging in age from 24 to 60, due both to natural and to artificial causes, in which androgen (testosterone propionate) was administered by intramuscular injection. The patients suffered from headaches, flushes, sweats and nervous upsets. Eighty per cent of the patients improved within two to three weeks after the weekly administration of 30 to 50 mg. of testosterone propionate. There was no effect on the breasts,

but 1 patient with arthritis was benefited and a woman aged 40 who was sensitive to estrogen by intramuscular and oral administration displayed no unfavorable reaction to androgen. PALMER, Philadelphia.

EFFECT OF TESTOSTERONE PROPIONATE ON URINARY EXCRETION OF ANDROGENS AND ESTROGENS IN EUNUCHOIDISM. W. H. HOSKINS, J. R. COFFMAN, F. C. KOCH and A. T. KENYON, Endocrinology **24**:702 (May) 1939.

According to Hoskins and his co-workers, the daily intramuscular injection of 25 mg. of testosterone propionate for periods of from nine to fourteen days brought about rises in the urinary androgens of 4 eunuchoids from basal levels of from 2 to 16 international units a day to from 44 to 115 international units and of urinary estrogens from the equivalent of 0.3 to 5 micrograms a day to that of 5 to 15 micrograms. This constitutes a restoration to normal values for both groups of substances. Both androgen and estrogen values fell toward pretreatment levels when medication was stopped. The changes in androgen and estrogen excretion paralleled the physiologic effects of testosterone propionate in the organism. Of 3 patients for whom the cause of the hypogonadism was unknown the extent of recovery of administered testosterone was 65, 49 and 49 per cent, respectively, on the assumption that half of the excreted material by weight is androsterone and half dehydroandrosterone. The recovery was 20 per cent for a patient whose pituitary was damaged by a suprasellar cyst. The rise in urinary estrogens to normal values following the administration of androgen suggests that the urinary estrogens of normal male urine may be derived in part from the metabolism of the testis hormone. However, the increase in the excretion of estrogen represents only 0.06 per cent of the androgen injected. J. A. M. A.

THE CLINICAL USE OF SYNTHETIC MALE SEX HORMONE [ANDROGEN]. H. H. TURNER, Endocrinology **24**:763 (June) 1939.

Turner reports the results of treatment of 54 patients with varying degrees of genital hypoplasia or sexual malfunction, ranging in age from 7 to 75 years. Fifteen cases are reported in some detail; of these, 11 were cases of hypogenitalism, 2 of impotence and sexual decline, 1 of prostatic hypertrophy and 1 of gynecomastia. Androgenic therapy consisted of intramuscular injections of testosterone propionate two or three times a week in doses of from 10 to 25 mg. From 10 to 75 mg. weekly was found to be effective in every case of hypogonadism, as evidenced by promotion of growth of hair, penile growth, production of erections and emissions, development of libido and sexual potency and generalized changes in the secondary sexual characteristics. Gynecomastia with normal secondary sexual development was apparently not influenced by injections of the synthetic hormone. In cases of diminution of sexual power associated with senescence, there was considerable relief of subjective symptoms of nervousness, irritability, insomnia, increasing fatigue, apprehension and gastrointestinal disturbances. In cases of benign prostatic hypertrophy there was clinical improvement, as evidenced by relief of symptoms and signs of prostatic obstruction. It was found that the subjective feelings were greatly improved, especially in cases of hypogonadal states. The mental attitude of the patients changed from one of shame and a feeling of inferiority to feelings of buoyancy, increased mental and physical activity and the development of a more aggressive masculine type of personality. In the hypogonadal persons there was definite evidence of prostatic growth. No untoward effects were noted in any of the patients treated. PALMER, Philadelphia.

EPILEPSY AS A PRISON PROBLEM: ITS TREATMENT WITH SODIUM DIPHENYLHYDANTOINATE. D. P. PHILIPS, J. Michigan M. Soc. **39**:317 (April) 1939.

Philips states that about a year ago 14 epileptic prisoners at the State Prison of Southern Michigan were given sodium diphenylhydantoinate as an anticonvulsant.

The drug, 0.1 Gm., was given three times a day before meals. The seizures of all but 1 patient were controlled by this regimen. This patient continued to have infrequent grand mal attacks at night, and his dose was increased to 0.4 Gm.. daily; that is, he received also 0.1 Gm. of the drug at 11 p. m. With the additional dose of the drug there have been no further convulsions. None of the patients had previously obtained any benefit from phenobarbital in large doses. With sodium diphenylhydantoinate therapy the convulsive seizures have ceased, and behavior and attitudes have improved. As yet there is no indication that the effectiveness of sodium diphenylhydantoinate is lost or diminishes with time. The depression which characterizes patients taking large doses of phenobarbital is noticeably absent with the use of sodium diphenylhydantoinate. The drug appears to offer a new hope of assistance in rehabilitation because of its ability to control epileptic seizures without a hypnotic effect.

J. A. M. A.

RESULTS OF A YEAR'S TREATMENT OF SCHIZOPHRENIA WITH INSULIN SHOCK. H. BAONVILLE, J. LEY, A. TITECA and J. TITECA, J. belge de neurol. et de psychiat. **39**:45 (Jan.) 1939.

The authors report the results of a year's treatment of 54 patients with schizophrenia at the neuropsychiatric center in Brussels. They were able to bring about a clinical cure in 21 cases, a social cure in 4 cases and partial remission in 8 cases. The condition was unchanged in 21 cases. They obtained a higher percentage of cures in paranoid than in hebephrenic or catatonic patients. They believe that in spite of the recent introduction of the method and the short period of observation, the treatment of dementia praecox by hypoglycemic shock constitutes the most important advance in psychiatry since the introduction of malarial therapy for dementia paralytica.

DE JONG, Ann Arbor, Mich.

CONVULSION THERAPY IN SCHIZOPHRENIA. L. VON MEDUNA, J. belge de neurol. et de psychiat. **39**:227 (April) 1939.

Meduna believes that metrazol therapy is much less dangerous than insulin shock treatment, as it is accompanied by a mortality rate of only 0.22 per cent, while for insulin therapy the rate has been reported as 4 per cent. Insulin therapy is a complicated procedure and requires the constant attention of a trained attendant and a physician for four or five hours during each treatment, while metrazol therapy can be carried out without special preparations and one physician and two attendants can treat from twenty to twenty-five patients in one hour. The cost per patient is four times as great with insulin as with metrazol. The results of metrazol therapy for schizophrenia in 56 clinics and hospitals in Europe through the month of August 1938 are as follows: Of 2,326 patients treated, 20 per cent have had remissions; 52.2 per cent of patients with acute conditions, of less than one and one-half years' duration, have shown remissions. Patients treated in 46 clinics and hospitals outside Europe through August 1938 numbered 1,751. Of these, 22.7 per cent have had remissions, and 35.2 per cent have shown considerable improvement. Patients with acute forms, of less than a year's duration, numbered 244, with 50.8 per cent showing remissions and 20.4 per cent improvement.

DE JONG, Ann Arbor, Mich.

TREATMENT OF ACUTE ANTERIOR POLIOMYELITIS WITH CEREBROSPINAL SERUM FROM CONVALESCING PATIENTS. R. MEYER, Rev. franç. de pédiat. **14**:517, 1939.

Meyer reports the use of cerebrospinal fluid from convalescing persons in the treatment of 13 unselected children in the child clinic of Strasbourg, Alsace-Lorraine. The children, who ranged in age from 5 months to 5 years (1 was 10 and 1 12), had entered the clinic before the seventh day of their illness, with fever. The first day from 30 to 50 cc. was injected, half intravenously, half intramuscu-

larly. On the following two days another injection was made of about 33 cc.—in all about 100 cc. The author advises preliminary intravenous injection of a hypertonic solution of a salt such as sodium chloride in grave cerebral conditions. Among the advantages of his cerebrospinal serum treatment the author mentions the facility of lumbar puncture and the possibility of immediate use. The fluid does not induce shock reaction and is easily preserved from spoiling. It is more readily obtained from convalescents than from discharged former patients. It can be extracted from infants every two weeks, and if necessary, after the acute stage, every week, without danger. To appreciate the therapeutic results obtained, the author explains, one must bear in mind the capricious evolution of poliomyelitis from the point of view of functional prognosis. The functional and the vital prognosis are more or less independent of each other except when the localization of the lesion is concerned. The two leading factors that control functional prognosis are the duration of the period of invasion and the time during which paralysis establishes itself. No tabular statement could be made for this because, the author says, in all cases in which he treated with the cerebrospinal serum of convalescent patients evolution ceased in less than twenty-four hours. He thinks that cerebrospinal serums from former patients are not so productive of results as serums from convalescing persons. The author includes in his paper the considerations that first led him to use this serum, his experimentation on animals, his observations antecedent to its use and his method of obtaining the serum. J. A. M. A.

THERAPEUTIC ACTION OF SODIUM CHLORIDE. S. DONTAS, Confinia neurol. **2**:46, 1939.

Dontas has used various concentrations of sodium chloride intravenously in the treatment of epilepsy, schizophrenia and other diseases of the nervous system. He states that intravenous injections of hypertonic solutions of sodium chloride have a sedative effect by producing dehydration of the nerve cells, with resulting decrease in excitability. Hypotonic solutions cause increased irritability, owing to hydration of the nerve cells. In epilepsy there is an immediate decrease in the frequency of the attacks following treatment with hypertonic solutions of sodium chloride; by this treatment, also, excited stages of schizophrenia and acute mania may be controlled. Hypertonic solutions may bring about improvement in parkinsonian states. Hypotonic solutions, on the other hand, have a favorable influence in depressions. DE JONG, Ann Arbor, Mich.

Special Senses

THE EFFECT OF VITAMIN A DEFICIENCY UPON THE RETINA OF THE RAT. MYRA L. JOHNSON, J. Exper. Zoöl. **81**:67 (June) 1939.

Droplets first described by Kolmer and supposed to be associated with visual purple are not present in the retinas of rats suffering from severe vitamin A deficiency. Moderate deficiency produces degenerative changes in the retina, such as friability of the outer segments of the rods in the periphery and complete degeneration of them in the fundus. In severe deficiency marked, progressive degeneration appears, beginning with the outer segments of the rods and involving in order the following structures: the inner segments of the rods, the external limiting membrane, the outer nuclear layer, the epithelial pigment layer, the outer molecular layer and the internal nuclear layer. Retinal rosettes occur in the differentiated retinas of rats with vitamin A deficiency, and are probably formed by the curling up of normal cells to fill the empty spaces caused by the resorption of degenerate cells. WYMAN, Boston.

RETROBULBAR NEURITIS WITH PELLAGRA IN NIGERIA. D. F. MOORE, J. Trop. Med. **42**:109 (April 15) 1939.

Moore discusses a syndrome that occurs extensively in southern Nigeria. It consists of perlèche, soreness of the tongue and genitalia and retrobulbar neuritis associated with optic atrophy. The condition has responded dramatically to treatment with autoclaved yeast products, and so is believed to be pellagrous. It is believed that gari, a dried, parched manioc food, plays an important part in its incidence. The facts in support of pellagra as the cause of the syndrome in southern Nigeria are that (1) throughout the palm oil belt there is an abundance of cheap edible oil, (2) no single case of xerophthalmia has been seen in southern Nigeria, (3) there is a great relative shortage of animal and fish protein in southern Nigeria (it is in these areas, or under conditions that permit this shortage, that this syndrome is found) and (4) when gari is eaten to excess in the absence of the protein protective foods it is shown to have an almost constant relationship to the incidence of this syndrome. Gari bears a strong suggestive comparison with "spoiled maize." A nutritional policy based on the recommendations of the League of Nations Health Committee (1937) is required for Nigeria to include particularly the development of local food sources and when possible to abolish by replacement both gari and stockfish as dietary essentials of the people. J. A. M. A.

CLAUDE BERNARD-HORNER SYNDROME AND OCULOSYMPATHETIC DISTURBANCES ASSOCIATED WITH LESIONS OF THE THALAMUS. RAYMOND GARCIN and MARCEL KIPFER, Rev. neurol. **71**:121, 1939.

Since the investigations of Pourfour du Petit, in 1727, demonstrated that stimulation of the intercostal nerves in animals resulted in dilatation of the pupils, the path of pupil-dilating stimuli has been traced by many workers. At present the path is known to extend from the hypothalamus through the substantia reticularis of the brain stem, the ventrolateral column of the cervical portion of the cord, the first and second thoracic ventral roots and the corresponding rami communicantes, the cervical portion of the sympathetic chain, the jugular twig of the sympathetic trunk, the nasociliary nerve and the long ciliary nerves to the iris. Does the pupil-dilating path begin oral to the hypothalamic center of Karplus and Kreidl? These authors expressed the belief that their center was part of a path from the frontal pole to the cervical portion of the sympathetic chain. In 1931 Guillain, Garcin and Mage observed a typical Bernard-Horner syndrome associated with a thalamic hyperalgic syndrome. A number of stimulation experiments performed by previous authors pointed to a pupil-dilating function of the medial nucleus of the thalamus. The present study employed bipolar electrolysis. Thirty-one dogs were used; 3 experiments are reported in detail. In these 3 cases there were pure thalamic lesions, and the animals survived from fourteen to thirty-nine days. The lesions were situated, respectively, in the dorsolateral part of the thalamus, the dorsal area and the dorsal part of the lateral nucleus. In all 3 cases there was ipsilateral miosis, associated in the first 2 instances with widening of the palpebral fissure. In the third case serial sections revealed, in addition to the thalamic lesion, microscopic lesions of the ipsilateral, lateral and medial geniculate bodies. The hypothalamus and brain stem were not involved. Other cases, in which false routes were produced, served as controls. Thus, a hemispheric lesion, lesions limited to the head of the caudate nucleus, lesions of the occipital horn and intraventricular hemorrhage had no lasting effect on the diameter of the pupil. In all cases the pupillary diameter was measured with a pupillometer. In only 1 dog did a hemihyperalgic syndrome follow injury to the thalamus, and in this case it was associated with a massive lesion of the cerebral cortex. In addition to the case in man reported by Guillain, Garcin and Mage, 12 cases of thalamic syndrome associated with anisocoria have been collected from the literature. In many of these cases, unfortunately, there were extrathalamic in addition to thalamic lesions. The case of Lhermitte and Fumet

is particularly demonstrative. The patient had a left hyperalgic syndrome, and the right pupil was wider than the left. The lesion involved the lateral nucleus of the right thalamus. The hypothalamus, midbrain and medulla were intact; the pons contained a few microscopic foci of disintegration. Some experimental results suggest that there may be a more direct pupil-dilating path from the thalamus than the long route via the hypothalamus, brain stem, spinal cord and sympathetic centers.

LIBER, New York.

TRANSITORY SPASMODIC MYOPIA CAUSED BY THE USE OF ACETARSONE. JEAN-SÉDAN, Rev. d'oto-neuro-opht. **17**:112 (Feb.) 1939.

Jean-Sédan reports 3 cases of spasmodic myopia occurring during the administration of sodium acetarsone. This toxic action occurred usually after the injections had been repeated over a considerable period. The myopia appeared after a few injections of the series and disappeared in two or three days. There were no accompanying symptoms of general intoxication, and the sphincter of the iris was not affected, contrary to experience with toxemia from the use of neoarsphenamine. Jean-Sédan has never observed neuritis or atrophy of the optic nerve in these cases. It seems certain that cases of spasmodic myopia of arsenical origin are rare, but many of them are overlooked by reason of the age of the patient.

DENNIS, San Diego, Calif.

PATHOLOGIC CORRELATION OF OCULAR MOVEMENTS. L. HALPERN, Confinia neurol. **1**:362, 1938.

Halpern describes two phenomena in which there is pathologic correlation of movements of the eyes. The first of these consists in consensual elevation of the lower lid on illumination of the contralateral eye. This condition occurs in coma, and Halpern believes that it is a defense reaction and assumes that its pathway lies in the subcortex. The second phenomenon consists of spastic closure of the eyelids on one side on voluntary movement of the eyeballs to that side. He believes that the association between lateral gaze and closing of the eyelids is due to irradiation of an impulse from the area regulating movements of the eyes to the area which controls the facial musculature.

DE JONG, Ann Arbor, Mich.

Diseases of Skull and Vertebrae

OSTEOMYELITIS OF THE FRONTAL BONE. RICHMOND MCKINNEY, Arch. Otolaryng. **28**:1 (July) 1938.

Eight cases of osteomyelitis of the frontal bone are reported from a total of 12 cases seen in the last two years. The patients ranged in age from 13 to 40 years. The infection was chiefly staphylococcic and extended through the diploe, with edema, a low grade septic fever or no fever. The diagnosis was made in a number of the cases from the clinical symptoms alone, without microscopic evidence of pathologic changes in the bone. Conditions diagnosed as chronic frontal sinusitis are frequently osteomyelitis. Although the amount of bone to be removed is at times appalling, the operation must be thorough and all such bone removed; otherwise recovery will not take place. Three of the 8 patients died, 1 of meningitis, 1 of abscess of the brain and 1 of bronchopneumonia.

HUNTER, Philadelphia.

POST-TETANIC GIBBUS: A PARADOXICAL SYMPTOM COMPLEX. CARL W. RAND, Bull. Los Angeles Neurol. Soc. **3**:141 (Dec.) 1938.

Rand reports the occurrence of varying degrees of collapse of the bodies of the midthoracic vertebrae in 3 children who had had tetanus. In the first case a girl aged 12 recovered from tetanus after the administration of antitetanus serum.

Roentgenograms made six months later revealed kyphosis with marked narrowing of the fifth, sixth and seventh thoracic bodies. Weight bearing subsequent to the disease was thought to be a potential factor. The second case was that of a boy aged 9 years who recovered from tetanus after the use of serum and showed the same deformity in lesser degree two weeks after the onset of the disease. In the third case a girl aged 7 had kyphosis and marked compression of the bodies of the fifth, sixth, seventh and eighth vertebrae immediately after recovery from tetanus. The mechanism producing the deformity is obscure, but important factors include immediate fracture induced by convulsive contractions of the flexor muscles of the spine and the later effect of weight bearing on vertebrae weakened by trophic changes. A few pathologic studies have revealed destruction of bone trabeculae and hemorrhage into the bone or between the vertebrae and the disks. Treatment should include rest in bed on a Bradford frame after recovery from the tetanus.

MACKAY, Chicago.

VERTEBRAL HEMANGIOMAS, WITH SPECIAL REGARD TO COMPLICATIONS AND ROENTGENOLOGIC DIAGNOSIS. A. SCHEEL, Norsk mag. f. lægevidensk. **1**:854 (March 25) 1939.

Scheel says that vertebral hemangiomas, frequently observed on anatomic examination, rarely give clinical symptoms. Only 36 cases in which neurologic symptoms were due to vertebral hemangiomas have been reported in the literature, and he adds 2 personal cases. Compression of the medulla, established in 31 cases, was most often caused by hemangiomatous masses in the epidural space which had broken through the vertebral body or arch. In 7 cases the only symptom was pain in the back, in part radiating to the abdomen and lower extremities. The symptoms of compression or pain appeared in both old and young. The youngest patient was 15; the most marked symptoms were felt by patients about 20, and pain as the only symptom was observed in older patients. The neurologic symptoms as a rule begin with weakness in the lower extremities; paresthesia and pain generally follow, and walking becomes difficult. Spastic paralysis may develop into complete paralysis. Often paralysis of the bladder occurs early in the course. Occasionally the condition remains stationary. Usually there is progression in the course of months or years. The outcome is often fatal. During life the diagnosis of vertebral hemangioma can be made only roentgenologically. The roentgenogram that corresponds to the anatomic condition shows a characteristic coarse-meshed structure. A vertebral hemangioma with neurologic symptoms calls for surgical or roentgenologic treatment. Operative treatment consists of laminectomy of the affected vertebrae and eventually also removal of the hemangiomatous tissue, which often extends epidurally. Improvement follows in from a few weeks to months. Fifteen patients with vertebral hemangiomas associated with symptoms of compression were operated on, with recovery or improvement in 8 instances, no change in 2 and death from hemorrhage from the hemangiomatous tissue in 5. Eight patients were given roentgen treatment, with marked improvement in 7 instances and no change in 1. Two patients were treated with radium, with marked improvement. According to Lievre, roentgen treatment should be reserved for the milder forms with pain as the only symptom, operative treatment being indicated in cases in which there is paralysis of greater degree, in spite of the danger of hemorrhage. The author says, however, that some degree of compression of the medulla was present in 4 of the patients treated roentgenologically, and he feels that roentgen treatment, and especially powerful radium treatment, might well be tried in cases of graver compression, if life is not in immediate danger. His 2 patients, women aged 73 and 56 with symptoms of pain, had favorable results from radium and roentgen treatment, respectively. The cases from the literature are tabulated in detail.

J. A. M. A.

Society Transactions

AMERICAN ASSOCIATION OF NEUROPATHOLOGISTS

J. W. KERNOHAN, M.D., *President, in the Chair*

Annual Meeting, June 5, 1939

TOPOGRAPHIC AND HISTOLOGIC IDENTITY OF THE EXPERIMENTAL (AVITAMINOTIC) LESIONS OF WERNICKE WITH LESIONS OF HEMORRHAGIC POLIOENCEPHALITIS OCCURRING IN CHRONIC ALCOHOLISM IN MEN. DR. LEO ALEXANDER, Boston.

Wernicke's hemorrhagic polioencephalitis can be produced with significant regularity as a complication of beriberi if vitamin B_1–deficient pigeons are given disproportionately ample supplies of other vitamins (A, B_2, C and D). If the pigeons are kept on an entirely vitamin-free diet, the resulting beriberi will only rarely be complicated by lesions of the Wernicke type. Wernicke's disease cannot be produced in pigeons which are receiving crystalline vitamin B_1 (thiamin chloride), though they may be deficient in all other vitamins or in any other vitamin for a period of over six months.

These observations suggest that vitamin B_1 posseses antiangiodegenerative as well as antineuritic properties, and that smaller amounts of vitamin B_1 are sufficient to act as an antiangiodegenerative agent than as an antineuritic agent.

The administration of high doses of vitamins A, B_2, C or D in cases of vitamin B_1 deficiency probably raises the vitamin B_1 requirement of the tissues, and angiodegeneration manifests itself soon after the onset of the neuronal degeneration.

The resulting characteristic angiodegeneration with varicose deformities of the vascular bed is the primary change in experimental Wernicke's disease in the pigeon, as well as in the disease associated with chronic alcoholism in man. The resulting subacute necrosis of the tissue, with glial proliferation, is secondary in both instances. Topographic analogy of the lesions is as striking as the histologic identity; in both cases there is a characteristic predilection for certain nuclei of the brain stem, namely, the nuclei of the vagus nerve, the nucleus triangularis, Bechterew's nucleus of the vestibular nerve, the trochlear and oculomotor nuclei, the mamillary bodies and the periventricular nuclei of the thalamus and the hypothalamus.

DISCUSSION

DR. F. H. LEWY, Philadelphia: How does Dr. Alexander explain the fact that vitamin B_1 deficiency, which so far has been considered as exclusively connected with the peripheral nervous system, is involved in lesions of the central nervous system under the conditions here described? What is the explanation for the predilective location of hemorrhagic lesions in the nuclei of the floor of the third and fourth ventricles and in the mamillary bodies following vitamin B_1 deficiency?

DR. LEO ALEXANDER, Boston: The explanation of the first point mentioned by Dr. Lewy is probably that the lesions in the peripheral nervous system were the more obvious and, therefore, were more striking to the original observers. In studying the literature, I found, however, that Prickett described hemorrhages in the brain stem in some of his vitamin B_1–deficient animals. However, he failed to recognize the underlying vascular disease and its identity with Wernicke's disease in man.

The locations of predilection for Wernicke's lesions in the nuclei of the floor of the third and fourth ventricles, including the mamillary bodies and the periaqueductal region, cannot be explained except by the assumption that the vascular walls in this region depend on a greater amount of vitamin B_1 than vessels in

other regions of the brain. However, this topographic arrangement is sufficiently typical to be one of the points of diagnostic value in the recognition of Wernicke's disease in man and in animals.

CHANGES IN THE NERVOUS SYSTEM IN CARBON DISULFIDE POISONING. DR. B. J. ALPERS, Philadelphia.

There has been conflicting evidence concerning the changes in the nervous system in carbon disulfide intoxication. Studies on human subjects have been relatively few and indefinite. The most important researches are those of Quensel and Abe. The former found scattered loss of ganglion cells with proliferation of endothelium in the vessels of the brain, and the latter observed scattered loss of ganglion cells, nonspecific changes in the nerve cells and mild changes in the basal ganglia. Of the 2 patients whose cases are reported in this paper, 1 died of uremia and the other after an operation on the gallbladder. In the first case there were marked arteriosclerosis of the cerebral arterioles and patchy loss of ganglion cells, particularly in the frontal areas; cell sclerosis; disease of the cells of the pallidum, cortex and putamen, and evidence of peripheral neuritis. In the second case there was relatively little except neuritis, the cortical changes being minimal.

Carbon disulfide does not produce specific changes in the brain. In the cases which have been reported, and in the cases submitted here, the lesions can be attributed to the carbon disulfide only by inference; it is probable, however, that the changes in the peripheral nerves are the direct result of the carbon disulfide poisoning.

DISCUSSION

DR. ARMANDO FERRARO, New York: Has Dr. Alpers had any experience with experimental lesions in cases of carbon disulfide poisoning? If he wished to carry on experimental work what type of animal would he choose? The questions seem to me pertinent, as the choice of animal is important in the evaluation of the pathologic changes. It is known, for instance, that while experimental lead poisoning produces in dogs a definite endarteritic reaction, the same reaction is absent in cats, and that in experimental insulin intoxication vascular pathologic changes were lacking in cats, whereas in dogs definite proliferative changes of the vascular system have been reported. At the New York State Psychiatric Institute, my associates and I are at present experimenting on cats with carbon disulfide poisoning, but we are in no position as yet to report on the pathology of such a condition.

DR. B. J. ALPERS, Philadelphia: As I mentioned, the data which I have reported relate exclusively to human pathology. Dr. Lewy is now carrying on experimental work on carbon disulfide intoxication and is using dogs as material.

EXPERIMENTAL DISSEMINATED ENCEPHALOPATHY IN THE MONKEY. DR. ARMANDO FERRARO and DR. GEORGE A. JERVIS.

This article will be published in full in a later issue of the ARCHIVES.

SYPHILITIC CEREBRAL HYPERTROPHIC PACHYMENINGITIS. DR. GEORGE B. HASSIN and DR. HOWARD ZEITLIN, Chicago.

This article will be published in full in a later issue of the ARCHIVES.

STUDY OF BLOOD VESSELS IN EPILEPTOGENIC FOCI. DR. STORER PLUMER HUMPHREYS, Newbury, Mass.

This study is concerned with the vascular supply of epileptogenic foci. The perivascular nerve supply and the structure of the walls of vessels removed from focal lesions of the brain which have been proved to cause recurring seizures were considered. Etiologic factors in production of the focal lesions were cerebral laceration, arterial occlusion, temporary ischemia, healed abscess of the brain and

meningitis. The vessels were removed from the specimens under the dissecting microscope and impregnated with silver by the use of a strong protein silver method.

It was found that vessels removed from all types of lesions were essentially the same. A study of the vessel walls revealed no disease of the musculature. The muscles were disposed in the normal two layer arrangement, an outer circular and an inner longitudinal layer. The only variation from the normal detected was thickening of the walls in vessels removed from tough connective tissue scars. Vessels from all types of foci were well supplied with perivascular nerves. These nerves were distributed to the vessels in a normal manner in two complexes, one outside the adventitia and the other just outside the media. The fibers were gathered into trunks, which gradually broke up in anastomoses, forming a network. Throughout the specimen there was a constant variation in a complex of nerve fibers composed of larger trunks than are seen in the normal intracerebral blood vessels. The morphologic character of the nerve fibers was entirely normal, all fibers being of the threadlike variety, with moniliform swellings irregularly distributed along their course. Each fiber was invested with a sheath, which in turn was supplied with Schwann nuclei. The fibers satisfied all the criteria for vasomotor nerve fibers elsewhere in the body. Nerve fiber counts per unit of vessel length showed a consistent increase in the number above normal. All counts were at the very upper limit of normal or above. From this study it is thought justifiable to state that there is a definite increase in perivascular nerve fibers to the vessels of epileptogenic foci.

DISCUSSION

Dr. Stanley Cobb, Boston: I am much interested in this paper of Dr. Humphreys, because I was recently in Montreal and looked over the actual specimens with him. I was greatly impressed by both the quantity and the quality of the work. The two important points seemed to be, first, that epileptogenic scars are more vascular than had previously been believed and, second, that the vessels in these scars have an abnormally rich innervation of autonomic nerve fibers. Both of these facts suggest an explanation of the trigger points observed at operation and of the improvement caused by removal of such points.

Moose Encephalitis. Dr. Lester S. King, Princeton, N. J.

Subacute or chronic leukoencephalitis occurring naturally in moose is described. The characteristic picture consists of a mild degree of perivascular demyelination, with formation of neutral fat and fibrous gliosis disproportionate in extent to the loss of myelin. There may be mild inflammation, restricted to the white matter. There is suggestive evidence that a primary inflammatory reaction, involving gray matter, observed in 1 of 8 animals, may represent a distinct condition. Attempted passage through animals of fresh material in 1 case was unsuccessful. The cause of this leukoencephalitis is obscure, although various possibilities are discussed.

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Diffuse Tumors of the Spinal Cord: Report of Two Cases. Dr. K. Löwenberg, Ann Arbor, Mich.

Two cases of tumor of the spinal cord, with duration of the disease for fourteen and twenty-six years, respectively, were presented, and the relationship to syringomyelia was discussed.

Case 1.—A boy aged 14, with spastic paraplegia, at the age of 2 years had complained of pain in the upper thoracic portion of the spine; at the age of 6 increasingly severe scoliosis appeared. In the following six years there was gradual development of spastic paraplegia.

Histologic examination revealed a diffuse tumor involving the spinal cord from the medulla to the lumbar region, associated with multiple cavities and diffuse glial proliferation. This tumor was regarded as an astrocytoma.

CASE 2.—A white woman aged 26 had complained of spastic paraplegia since early childhood. Neurologic examination revealed kyphoscoliosis, deformity of the thorax, complete paraplegia, diminished sensibility beginning below the seventh cervical dermatome, hydrocephalus and "automatic bladder." Histologic examination revealed multiple cavities and tumor elements throughout the cord.

DEMONSTRATION OF SCHWANNIAN ORIGIN OF TUMORS OF THE NERVE SHEATHS. DR. MARGARET R. MURRAY, New York.

In investigating the cellular origin of the specific nerve sheath tumor, my colleagues and I have attacked the subject by the method of tissue culture, in the hope of obtaining critical evidence which the purely histologic approach has failed to reveal.

The procedure was: (1) to cultivate normal and experimental nerve sheaths in vitro, with study of the morphologic and physiologic character of the outgrowing cells, and thus to assemble a set of criteria by which the Schwann cell may be distinguished from its accompanying fibroblasts, under conditions of uncontrolled or unorganized growth; (2) to obtain spontaneous tumors of the nerve sheath and cultivate them under similar conditions, comparing the outgrowth with the norms established in the preceding experiments.

1. In the study of normal and experimental nerve sheaths we cultivated normal spinal nerves of man and the rat and tumors formed after sectioning the sciatic nerve. When one is dealing with a normal nerve in culture it is possible to identify the Schwann cells in the explant, as they assist at wallerian degeneration, and to observe them as they emerge in alinement from tufts or nerve fibers. Since they have a characteristic morphologic appearance and definite staining peculiarities, it is possible to recognize them when they are free and isolated in an outgrowth composed of all the constituents of the nerve sheath. The same general morphologic features characterize the outgrowths from the experimental tumors.

2. We cultivated two sets of spontaneous tumors from different subjects and found them to be composed of Schwann cells. The outgrowth from the A areas (Antoni, N. R. E.: Ueber Rückenmarkstumoren und Neurofibrome, Munich, J. F. Bergmann, 1920) was highly typical; it was comparable in all particulars with the schwannian outgrowth from the normal nerves and was wholly different from the endoperineural fibroblast. The outgrowth from the B areas was marked by aberrance of the digestive function which the Schwann cell normally possesses. The B cell liquefied its fibrin clot to such an extent that its fine processes were retracted for lack of solid support and its form was often distorted. The analogue of microcystic degeneration can thus be observed in progress, though when the medium is renewed, as in vitro, the cell does not degenerate, but survives indefinitely.

PERINEURIAL FIBROBLASTOMAS: DIRECT STAINING EVIDENCE AGAINST THEIR SCHWANN CELL ORIGIN. DR. I. M. TARLOV, Brooklyn.

The hypothesis of the schwannian origin of the common encapsulated tumor of nerves was put to test by a direct staining method for Schwann cells—Dockrill's modification of del Rio-Hortega's silver impregnation technic. By means of this technic Schwann cells which occur along the nerve fibers in neurofibromas of the von Recklinghausen type were clearly impregnated, whereas the type cell of this tumor, which is the same as the type cell of the solitary tumor (perineurial fibroblastoma, schwannoma, neurinoma or neurilemmoma), proved to be of a totally different type—elongated like a fibroblast. The contrast between the Schwann cell of the nerve fiber and the type cell of the tumor was clearly shown in a single microscopic field. The technic was applied directly to the solitary encapsulated tumors, the cells of which proved to be elongated like fibro-

blasts and totally unlike Schwann cells. By means of this technic, proliferating Schwann cells which occurred in a traumatic neuroma of the ulnar nerve were clearly impregnated. The inability to impregnate Schwann cells in the solitary encapsulated tumor of nerves by this technic, which brings out normal and proliferating Schwann cells, is considered as valid evidence to disprove the schwannian origin of these tumors. The fibroblastic origin of these tumors is accepted in view of the clear morphologic resemblance of the type cell to fibroblasts and the rich reticulin stroma which suggests the endoneurium. Attempts to show that reticulin formation may be provoked by Schwann cells are not considered conclusive. For example, Masson (Experimental and Spontaneous Schwannomas [Peripheral Gliomas], *Am. J. Path.* **8**:367, 1932), as evidence to support the view that Schwann cells may provoke the formation of reticulin without the intervention of fibroblasts, cited Nageotte's demonstration (Sheaths of the Peripheral Nerve, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 1) that reticulin occurs along the central prolongations of nerve fibers throughout the pial ring in the same distribution as in the membrane of Schwann. Nageotte expressed the opinion that fibroblasts do not occur in this region and hence that they are not necessary for the formation of reticulin. However, I (Structure of the Nerve Root: I. Nature of the Junction Between the Central and the Peripheral Nervous System, ARCH. NEUROL. & PSYCHIAT. **37**:555 [March] 1937) pointed out that this argument is not valid, since I was able to demonstrate fibroblasts central to the pial ring with the same distribution as reticuluin. The fibroblast is constantly found in association with reticulin of the endoneurium.

Although endoneurium may give rise to these tumors (as indicated by their occurrence in 2 cases along portions of the vagus nerve roots, which are devoid of perineurium), it seems wise, in order to avoid further confusion that might arise from the introduction of a new term, to retain Mallory's name perineurial fibroblastoma (The Type Cell of the So-Called Dural Endothelioma, *J. M. Research* **41**:349, 1919-1920). Nerve fibers within an encapsulated tumor of peripheral nerves, although ordinarily characteristic of multiple neurofibromatosis, were encountered within one of the solitary perineurial fibroblastomas of the vagus nerve which was reported.

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DISCUSSION ON PAPERS BY DR. MURRAY AND DR. TARLOV

DR. ARTHUR WEIL, Chicago: Since I have been following this controversy about the origin of the cranial nerve neurinoma, I have wondered why such a dogmatic point of view should be taken. Though good supporting evidence was presented by each side, each insisted on either the fibroblastic or the Schwann sheath cell origin of these tumors. If one takes the example of the meningiomas, it is apparent that not only mesothelial cells but also fibroblasts and blood vessels become neoplastic. The changing proportion of these different elements forming the meningiomas had led Bailey and Bucy (The Origin and Nature of Meningeal Tumors, *Am. J. Cancer* **15**:15, 1931) to an attempt to classify them accordingly. In glioblastoma multiforme one sees frequently excessive capillary proliferation with the neoplastic disease of the glia, and, contrary to the opinion prevalent concerning this group, French pathologists refer to it as *angio-gliom*. In the cranial nerve neurinomas there is in the proximal part of the root, beyond the borderline of the connective tissue endoneurium, neoplastic disease of the glia, which may vary from an astrocytoma, with admixture of spongioblast-like cells, to mild glial proliferation. Why, then, should one be opposed to the idea that in the distal part of the same nerve both Schwann sheath cells and fibroblasts may become neoplastic?

The problem cannot be settled by staining methods. It is known, for example, that the Davenport method ordinarily does not stain glia. But it stains distinctly glioblastomas and neoplastic glia under experimental conditions. A neoplastic

cell will have a different chemical and physicochemical makeup than its mother cell and, therefore, a different reaction toward dyes. Tissue cultures are more convincing evidence, though they are not conclusive. Since the problem at present seems not to be settled in favor of either the Schwann sheath cell or the fibroblast, it seems closer to reality to assume that in this tumor the same conditions prevail as in the meningiomas; both fibroblasts and Schwann sheath cells (and proximal glia) become neoplastic and, according to their relative prominence, manifold admixtures are found. The extremes are schwannomas (Recklinghausen's disease) and endoneurial fibromas (interstitial hypertrophic "neuritis").

DR. WILDER PENFIELD, Montreal, Canada: Dr. Tarlov has presented strong evidence from a structural point of view that these tumors are indeed made up largely of specialized fibroblasts. He has pointed out clearly that these tumors may arise from the endoneurium as well as from the perineurium, and in employing the term perineurial fibroblastoma one must now understand that the endoneurium is not excluded. This is, I think, what one might expect. He has brought all the evidence that specificity of staining can give that the Schwann cell and the oligodendroglia cell are analogous, and he has pointed out that both fibroblasts and reticulin fibrils stop at the frontier of the nervous system. Specificity of staining is difficult to rely on. A good stain, however, enables one who knows cellular morphology to recognize these cells.

I do not agree with the point of view that has been brought forward in the discussion, namely, that it does not matter much, so why worry, about the nature of the origin of the tumor cell. If one is to think clearly about histologic matters at all, one must be concerned with the type cell of tumors.

Dr. Murray's demonstration is extremely interesting and well done, and the evidence that she brings forward points strongly to a schwannian origin for these tumors. Is she quite certain that her culture technic does not discourage a growth of fibroblasts? Furthermore, I ask her to use the same technic with the meningeal fibroblastoma and fibroma and perhaps to report on her results next year.

DR. LESTER S. KING, Princeton, N. J.: There are a few points in Dr. Tarlov's paper to which I should take exception. The presence of extensive reticulin in these tumors in no way indicates that they are composed of fibroblasts. Although fibroblasts can form reticulin, there is abundant evidence that reticulin may be formed in the absence of demonstrable fibroblasts. In the nervous system the finest capillaries have an extensive reticulin framework, but fibroblasts cannot be demonstrated. In the demyelinating diseases, extensive reticulin nets may be present, again in the absence of demonstrable fibroblasts.

I think Dr. Murray should be congratulated on her brilliant demonstration. In view of the fact that fibroblasts, especially of neoplastic origin, are easy to grow in tissue culture, it is of great significance that her tissue cultures have shown an overhelming predominance of Schwann cells in the outgrowth.

DR. PERCIVAL BAILEY, Chicago: The contradictory reports of Dr. Murray and Dr. Tarlov leave me in doubt. Dr. Tarlov has impregnated sharply the Schwann cells in the nerve and also some cells in the tumors. However, the method he employed is not specific. It impregnates fibroblasts also in the same sections, and one is left in doubt concerning the nature of the cells impregnated in the tumors. On the other hand, Dr. Murray has grown two types of cells in her cultures, but one wonders whether they really are as different and distinct as the fibroblast and the cell of Schwann. The difference might be due simply to the fact that some are flattened against the cover glass and others growing free in the medium among the fibrin. I believe that the question is still open.

DR. LEO ALEXANDER, Boston: Dr. Tarlov's staining reaction is striking and helps to confirm the impression that I have gained by comparing tumors of the meningioma series with the so-called neurinomas. In many cases, particularly those of the large neoplasms of the olfactory groove, differential diagnosis is extremely difficult, if not impossible. In 1 case I was not able to make a differ-

ential diagnosis at all. Therefore, I have for some time followed Dr. Mallory (The Type of So-Called Dural Endothelioma, *J. M. Research* **41**:349, 1920). He considered both these tumors as fibroblastomas, one group being meningeal fibroblastomas and the other group perineurial fibroblastomas. In this connection, I wish to mention that reticulin outside the central nervous system is nothing but attenuated collagen; in the central nervous system, however, a reticulum of glial nature can be demonstrated.

Dr. Arthur P. Stout, New York: My first intimate contact with tumors of the peripheral nerve sheaths occurred in 1921, when Dr. Penfield came to the Presbyterian Hospital in New York and started to study them intensively. At that time I was an adherent of the fibroblastic origin of these tumors. This belief was shaken by the work of Nageotte and Masson (Nageotte, J.: Sheaths of the Peripheral Nerves: Nerve Degeneration and Regeneration, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932. Masson, P.: Experimental and Spontaneous Schwannomas, *Am. J. Path.* **8**:367, 1932), but it did not seem possible to adopt the schwannian hypothesis unreservedly on purely histologic evidence.

Dr. Murray's establishment of the cultural characteristics of schwannian cells and her demonstration that cells having exactly the same morphologic and physiologic peculiarities are the only ones which grow from explants of neurilemmomas offer what seems to me convincing evidence that these are schwannian tumors. Dr. Murray did not tell of an observation that seems to me to be of some significance. If a cotton fiber or fine glass filament is thrust into the explant, the cells which grow out invariably form a reticulated meshwork or sheath about the fiber. This phenomenon has not been observed with fibroblasts. Dr. Tarlov's contention is based on evidence which is of a negative character and depends on the reliability of a silver stain. Both of these facts seem to me to make them of insufficient importance to weigh against Dr. Murray's positive evidence.

Dr. Margaret R. Murray, New York: It has been suggested that the syncytial habit of the Schwann cells in vitro which I have described does not agree with Speidel's accounts of Schwann cells, which migrate as individuals. I should say that in vitro it is not unusual for them also to wander off singly from the group; they are often seen migrating in the outgrowth. Thus, they duplicate their behavior in early developmental stages, such as have been described by Harrison and by Speidel (Harrison, R. G.: Neuroblast Versus Sheath Cell in the Development of Peripheral Nerves, *J. Comp. Neurol.* **37**:123, 1924. Speidel, C. G.: Studies of Living Nerves: The Movements of Individual Sheath Cells and Nerve Sprouts Correlated with the Process of Myelin Sheath Formation in Amphibian Larvae, *J. Exper. Zoöl.* **61**: 279, 1932). The more common and characteristic arrangement is syncytial in my cultures, which are from more differentiated nerve sheaths, but both types of behavior may occur in the same culture. A single isolated cell may later produce its own syncytium by nuclear division without cytoplasmic separation.

I welcome Dr. Tarlov's work on specific silver staining of Schwann cells, especially since it seems to stain the tumor cells also. However, as Dr. Penfield has indicated, I do not believe one should expect a tumor cell, deprived of neurites and of its other normal relationships, to show the same morphologic features as a normal Schwann cell situated on a medullated fiber.

Dr. Penfield has brought up the question whether the medium I have used is one which discourages fibroblasts and favors other types of cells. There is no reason to believe that this is true. Normal adult human fibroblasts do not proliferate rapidly in the ordinary culture medium, it is true; but in cultures of the fetal and young rat material fibroblasts were numerous. I think that the neurilemmoma cells grow in our cultures not because they are Schwann cells or fibroblasts but because they are tumor cells.

Dr. I. M. Tarlov, Address: Cox and Cranage (*J. Path. & Bact.* **45**:477, 1937), from their study of various types of tumors in tissue culture, suggested that the tumors which are here being considered have a histologic structure

resembling what they called a fibroma, implying that the type cell was of the fibroblast series. This suggestion, however, was based on their study of only one such tumor.

The cells which Dr. Murray showed on the screen and identified as Schwann cells are smaller than those which she refers to as fibroblasts. This seems strange, since Schwann cells, in fixed and stained preparations, always appear larger than fibroblasts. It seems to me that those cells which were called Schwann cells possess the characteristic appearance not of Schwann cells but of fibroblasts.

The fact that these cells may differ somewhat in tissue culture from the usual fibroblasts which are encountered does not necessarily mean that they are not fibroblasts. It seems understandable that the fibroblasts of these tumors may be of a somewhat different type, since one finds them in a special environment—in the endoneurium. It is well known that cells of a given type—for example, oligodendrocytes—vary considerably in form, depending on the particular environment in which they occur.

I am aware that there have been many attempts to prove that reticulin is not necessarily related to fibroblasts. I do not know whether one can accept all the evidence. I do know, however, that with regard to the endoneurium where one finds reticulin one also finds fibroblasts.

With regard to the specificity of the Dockrill technic, which was used in this study, one may say that it is specific for Schwann cells in the sense that it impregnates these cells so clearly that they may be readily differentiated from other types of cells.

The criticism that I have drawn a positive conclusion from negative evidence is, I believe, not true. I have shown by clearcut staining evidence that the type cells of these tumors is not the Schwann cell. In these same preparations it has been shown that the type cell presents the morphologic characteristics of the fibroblast.

CHANGES IN AXIS-CYLINDERS AND OTHER PARENCHYMAL STRUCTURES IN MULTIPLE SCLEROSIS AND ALLIED CONDITIONS. DR. TRACY J. PUTNAM, New York, and DR. LEO ALEXANDER, Boston.

A comparison of preparations stained by the Weigert-Pal with those stained by the Bielschowsky technic is the usual basis for the statement that the lesions of multiple sclerosis consist essentially of areas of demyelination. The use of certain new stains gives a more accurate and detailed view of the situation. The Bodian stain (Bodian, D.: A New Method for Staining Nerve Fibers and Nerve Endings in Mounted Paraffin Sections, *Anat. Rec.* **65**:89, 1936) for axis-cylinders may be used with the Smith-Quigley (Smith, W. K., and Quigley, B.: A New Method for Rapid Staining of Myelin Sheaths, *Am. J. Path.* **13**: 491, 1937) and other stains for myelin on alternate sections. A comparison of the two sets of sections reveals that, even in early stages of the formation of a plaque, axis-cylinders are fragmented and degenerated. The loss of axis-cylinders is always less than that of myelin, not only in the plaques of multiple sclerosis but also in other lesions of vascular origin, and of comparable severity and age. The apparent contrast between the degree of involvement of the respective tissue elements is increased by an optical illusion which causes one to notice less the degree of diminution of small, sparse structures, and also by the fact that all stains employed for axis-cylinders also stain glia fibers to some extent.

In addition to the loss of myelin and damage to axis-cylinders, loss of minerals, decrease in glial protoplasm, loosening of glial reticulum and (usually) proliferation of glial nuclei are among the earliest changes in early plaques. They are also characteristic of early anoxic foci of any origin. The specific hypermineralization of infectious processes is missing in both conditions.

DISCUSSION

DR. LEO ALEXANDER, Boston: During the part of our work concerned with the preservation of axis-cylinders, we found that the appearance of preservation of axis-cylinders in multiple sclerotic plaques and other lesions, which is so

striking in the well known low power views, is frequently fallacious. Closer study of high power views and actual counts revealed not only severe pathologic changes, mostly shrinkage and thinning, but also a severe loss in numbers of axis-cylinders, frequently as severe as the loss of myelin sheaths. Experiments with optical patterns have convinced us that the appearance of preservation of axis-cylinders in certain lesions is frequently an optical illusion and may be obtained even in lesions due to simple wallerian degeneration, unless one resorts to the labor of counts under high power. It is emphasized that no assumption of preservation of axis-cylinders should be made from the inspection of pathologic specimens without comparative counts of axis-cylinders and myelin sheaths.

Attention is called to the work of Schmitt (Schmitt, F. O., and Bear, R. S.: The Ultrastructure of the Nerve Axon Sheath, *Biol. Rev.* **14**:27-50, 1939), who showed by ultramicroscopic and birefraction studies that the transition from the myelinated to the nonmyelinated fibers is a gradual one and that the degree of birefringence or the presence of myelotropic material is correlated with the diameter of the axon. This indicates that shrinkage and thinning of the axis-cylinder alone would account for demyelination of the axon.

In microincinerated preparations the myeloaxostroma, that is, the mineral ash–containing protein stroma, which pervades both the axis-cylinder and the myelin sheath, is an inseparable entity and receives further direct reenforcements from glial processes in the central nervous system and from schwannian cells in the peripheral nervous system. It is further shown that in early lesions of multiple sclerosis damage to the myelin sheaths, axis-cylinders and glial reticulum is synchronous. Demineralization of the glial reticulum and shrinkage, disintegration and loss of stainability of the normal glia in the lesion are the earliest features of the lesion of multiple sclerosis, and it is not until after some time that the glia recovers and reactive proliferation takes place. The early damage to the glia is always simultaneous with the damage to the parenchyma. This indicates that the lesion of multiple sclerosis is not selective, but affects all tissue elements of the diseased part simultaneously.

DR. FREDERIC WERTHAM, New York: Dr. Putnam's and Dr. Alexander's paper is an original and careful contribution to an important subject. It is one of the strange dogmas in neuropathology, which has persisted for a long time, that the axis-cylinders in multiple sclerosis are not affected. There are a number of reasons why this erroneous opinion has come about. There is no doubt in my mind that the Bielschowsky method at times stains glia fibers. The glial response in these lesions seems to me to be a reaction that may set in early as a response to the altered nutritional state and the altered consistency of the tissue. It will have been noticed in the extremely interesting paper by Dr. King on moose encephalitis that in some of his slides there was tremendous gliosis, while the myelin sheath pictures showed only relatively mild lesions. The methods, observations and interpretations of Dr. Putnam and Dr. Alexander not only are a contribution to the problem of multiple sclerosis but are of great interest to the general subject of the histopathology of nerve parenchyma.

DR. G. B. HASSIN, Chicago: There is much poetry in Dr. Putnam's presentations of the pathology of multiple sclerosis. While degenerative changes in axis-cylinders are undoubtedly present in this morbid condition, their evolutional stages cannot be followed as easily and as thoroughly as is the case in the myelin changes. This was evidently also Dr. Putnam's experience.

DR. T. J. PUTNAM, New York: Regressive changes in the axis-cylinders in multiple sclerosis and similar lesions take place more rapidly and less spectacularly than do those in the myelin sheaths. But though the evolution is rapid, it is definite and unmistakable, especially as demonstrated by the Bodian stain. I wish I could feel there was something creative in these observations, as Dr. Hassin implied. To my mind, they are decidedly prosaic—merely the application of a number of stains to a number of sections over a number of years and pictures of the results. I am sure that any one here would have seen the same things in the same preparations.

CHANGES IN THE MENINGEAL BLOOD VESSELS IN TUBERCULOUS MENINGITIS. DR. N. W. WINKELMAN and DR. MATTHEW T. MOORE, Philadelphia.

The blood vessels in tuberculous meningitis show involvement mainly of the inner and outer coats. The media and elastica usually play a passive role, and the changes in them depend on the pathologic lesions in the contiguous coats. The adventitial picture is usually part and parcel of the tuberculous process within the subarachnoid space. The intimal change is perhaps the most interesting and varied. Six types of changes have been selected by us as representative of the changes within this coat: (1) simple subendothelial inflammatory infiltration; (2) verrucous subendothelial inflammatory infiltration and proliferation: (*a*) without tubercle formation, and (*b*) with tubercle formation; (3) uniform concentric intimal proliferation (simulating Heubner's endarteritis); (4) intimal infiltration and proliferation with complete closure of the lumen of the vessel; (5) degeneration and caseation of the intima separately or in conjunction with the remaining tunics, and (6) intimal fibrinoid-hyaline change (Askanazy).

The most characteristic type of vascular change is the so-called panarteritis tuberculosa. We have found that this is only one of the many different forms which depend for their configuration on the chronicity of the meningeal process; the more chronic the process the greater the likelihood of the proliferative fibrotic changes resembling Heubner's endarteritis; the more acute the process the greater the tendency to the infiltrative manifestations without proliferation or degeneration. The age of the patient does not play a part in the type of pathologic lesion found; the duration of the disease is probably the most significant factor.

DETROIT SOCIETY OF NEUROLOGY AND PSYCHIATRY

JAMES M. STANTON, M.D., *in the Chair*

Regular Meeting, Nov. 10, 1938

DIAGNOSTIC DESIGNATIONS IN A GENERAL HOSPITAL. DR. T. J. HELDT.

Diagnostic designations are the labels one assigns to aberrant patterns of behavior, or distorted somatic reactions. These labels are helpful in grouping and classifying patients. The more informative the label, the more easily is it understood. The use of psychiatric nosologic designations and descriptive terms in a general hospital is not without interest. Neurologists and psychiatrists, especially the latter, have often been accused of using language quite foreign to the field of general medicine. Fifteen years ago, the internist, the surgeon and the pediatrician usually resorted to such words as "functional nervous disturbance," "neurotic," "hysterical" and "neurasthenic." More recently, one finds the words "psychoneurosis" and "psychosis," with increasing readiness to ask for psychiatric interpretation of manifestations. This reflects a need and, at the same time, a way of meeting it.

In delimiting the scope of neurology and psychiatry, the following six grand divisions have been followed: (1) nervous diseases and injuries; (2) the psychoses; (3) the psychoneuroses; (4) mental deficiencies; (5) constitutional psychopathies; 6) the inebrieties. Each heading may be subdivided at will and a nomenclature used that will fit statistically the requirements of state and federal records.

In the general hospital one deals with the first deviations in everyday adaptations. All the borderline morbidities come in review. Patients with psychoses also are admitted. It is evident, then, that the general hospital may receive patients with any neuropsychiatric disorder. How may psychiatrists record the first deviations from normal behavior so that medical confreres may understand them fully? Principally by using diagnostic terms, words and phrases with which they

are already familiar. If this admonition is heeded, the psychiatrist may occasionally use a word, phrase or even diagnosis with which these associates are not entirely familiar in the hope that he has won a degree of respect that will stimulate them to broaden their vocabulary. In my particular general hospital locale, the word "neurotic" has been allowed to stand without much condemnation; when called on to explain what is meant by "neurotic" one is apt to give a simple example, such as that of a person who uses a headache as an excuse to avoid attending a social function. If resort to such an excuse is frequently repeated the patient may be said to be experiencing neurotic exaggerations. If the use of neurotic exaggerations becomes habitual to the point at which the patient himself loses that discrimination that he first had in regard to a solicited symptom or sensation, and has yielded to it so many times that he is sure that he must possess the symptom complex in question, then one may safely say that he is experiencing neurotic fixations, whether they are a gastric, a cardiac or a cephalic group of symptoms. When a person formulates his neurotic exaggerations and fixations into more and more definite patterns, systematizing his reactions so that they actually serve a compensatory function and help him to meet situations otherwise intolerable, then one concludes that one is dealing with a psychoneurosis.

According to their patterns of formulation, I recognize six forms of psychoneurosis; those that cannot be placed in a definite pattern I call atypical. In three types of psychoneuroses the somatic references predominate. These are: the psychasthenic, the hysterical and the neurasthenic, with the observed frequency of approximately 2, 20 and 5 per cent, respectively. I recognize two forms of hysteria —the conversion and the anxiety type. There are three types of psychoneuroses in which psychic references predominate, viz., anxiety, hypochondriacal and traumatic (traumatic neurosis). The frequency of these is approximately 60, 2 and 5 per cent, respectively. That leaves a frequency of roughly 3 per cent for the atypical group.

In the field of mood changes I have also found it advisable to be cautious. Not infrequently there may be admitted to the general hospital a patient who has been overcome by sad bereavement or by having financial resources suddenly swept away. One often finds that such persons are not in the habit of showing this pattern of behavior—the depression is in keeping with the stimulus that brought it about. One may suspect a manic-depressive psychosis, but unless there is positive proof I prefer to designate such depression as symptomatic or reactionary. If the patient has experienced some type of mental depression previously, I not infrequently record that the patient may have a cyclothymic type of personality.

The designations problem child, personality inadequacies, handicapped personality, eccentric personality, schizoid personality and hypomanic personality, among others, may serve to bridge the gap that many physicians have so roundly condemned. I use the designations of statistical manuals when diagnostic deductions have been adequately corroborated by time and sufficient observation. I am, however, cautious not to let the mere presence of a delusion or a hallucination lead to a diagnosis of dementia praecox, or schizophrenia, even provisionally.

A patient in the general hospital is much more "common property" than is the patient in a special or in a state or county institution. No one can know when his note or diagnostic deductions may be quoted in a report or in a letter to an outside physician. Such a report may be made immediately, or several years later. For this reason, and many others, I have judged it wise to be not too rigid in the use of diagnostic terms, or too ready to pin on a label. There need be no curtailment of current standardization, but excessive surcharging of impressionistic data must be avoided.

PROTRUDED INTERVERTEBRAL DISKS. DRS. H. S. SANFORD and A. S. CRAWFORD.

Protruded intervertebral disks and associated encroachments on the cauda equina were the etiologic agents giving rise to lumbosacral and sciatic pain in 14 patients operated on at the Henry Ford Hospital during the past eighteen

months. All patients were male. Eleven had a definite history of injury to the back. All 14 patients complained of sciatic pain, this being on the right side in 7, on the left in 5 and bilateral in 2. Subjective numbness was noticed as a symptom by 9 patients, and local weakness, by 4. One man had experienced occasional urinary incontinence, and another, relative impotence.

The most constant neurologic finding was evidence of motor weakness, usually in the dorsiflexor muscles of the ankles, this being present in 12 of the 14 cases. There were objectively demonstrable sensory loss in 10 cases, a reduced ankle jerk on the side of the sciatic pain in 6 and absence of the ankle jerk in 5.

The values of the total protein in the spinal fluid ranged from 30 to 150 mg. per hundred cubic centimeters, the average for the group being 65 mg. The "reversed Queckenstedt maneuver," as advocated by Love, gave a positive reaction in only 4 instances.

Roentgenograms of the spine revealed a narrow interspace at the site of the lesion in 5 cases. The lesions were all demonstrable roentgenologically after the intrathecal introduction of 5 cc. of iodized poppyseed oil.

The diagnosis of protruded intervertebral disk does not necessarily indicate surgical intervention. These 14 cases do not include the entire number in which such a diagnosis has been made during this interval, as some patients responded adequately to nonoperative orthopedic measures. In our opinion, all patients should be given a thorough trial of conservative treatment before operation is advised.

Surgically, the problem has many aspects. In this paper we have considered only the factors which may result in pressure on or irritation of the spinal nerves as they pass through the intervertebral foramens. Anatomically, the important structures are (1) the intervertebral disks, (2) the ligamenta flava, (3) the articular facets and (4) other factors, such as dilated venous plexuses and anatomic constrictions of the spinal canal or intervertebral foramens. The first is the most common cause of trouble and may be the result either of chronic hypertrophy of the disk or of rupture of the annulus fibrosus and protrusion of the nucleus pulposus. The ligamenta flava may also be an important factor if they are hypertrophied or if there is an unusually thick interspinous ligament or a constricting lamina. Occasionally the intervertebral foramen is encroached on by the base of an unusually prominent facet.

In 9 of 14 cases in which operation had been performed at the time of this report, the condition was due to definite protrusions of disks, in 2 to prominent disks only and in 3 to other encroachments on the intervertebral foramens, chiefly, thickened ligamenta flava. The results thus far have been excellent in 4 cases, good in 5 and fair in 5; there have been no failures. From six to eighteen months have elapsed at the time of this report.

In summary, the neurosurgeon offers relief from pain to a definite group of patients who have previously not been relieved by various methods of therapy. In this group are all those in whom the spinal nerves are pressed on or irritated by one or several of the adjacent structures which may encroach on the intervertebral foramens. From the roentgenologic and clinical findings one cannot predict with any certainty, before the operation, which of the structures is the chief inciting factor. Adequate operative exposure permits this determination, and usually one or several apparently irritating or compressing factors can be removed, with relief of the pain in most cases. The results based on more experience over a longer period should permit more reliable conclusions. As has been said, we believe operation should be performed only after the patients have had a thorough trial of all feasible conservative measures.

NEUROLOGIC DISEASE ASSOCIATED WITH PERIPHERAL VASCULAR DISEASE. DR. G. O. GRAIN.

The common factor in all lesions of the nervous system is probably tissue anoxia. In the common vascular lesions of the central nervous system this results

from gross interference with the blood supply to neurons and supporting tissues in relatively large areas. The resulting gross tissue damage is in some degree irreversible, depending on the intensity and duration of the anoxia. It is recognized that gross cerebral vascular lesions may be of relatively short duration as a result of transitory occlusion, presumably due to spasm in an arterial wall. The manifestations of cerebral angiospasm in older persons with evidence of arterial disease are not unfamiliar. That gross angiospastic lesions may occur in relatively young persons with no evidence of arterial disease is illustrated by the case of a woman aged 38 with angiospastic phenomena affecting the fingers and one toe. Microscopic examination exhibited capillaries of the finger nail beds of moderate tortuosity with marked evidence of spasm, and the occlusion index test gave a curve suggestive of organic occlusion or prolonged spasm. Palpable arteries were normally elastic; the blood pressure was 175 systolic and 110 diastolic. Nine months later the patient returned with right hemiplegia, which disappeared in two weeks; the arterial hypertension had completely disappeared. In contrast to a condition of this type, there may occur slow degenerative lesions in the brain or spinal cord which are presumed to result from more chronic or repeated partial ischemia due to attenuated blood supply in arteriosclerotic persons, together with nutritional factors favoring tissue anoxia. In the peripheral nervous system one sees evidence of this type of ischemic anoxia in cases of diabetic neuritis, peripheral arteriosclerosis, thromboangiitis obliterans, periarteritis nodosa and proliferating intimitis. The common clinical condition found in these disturbances has been termed ischemic neuritis by recent writers. The common factor is obliteration of vasa nervorum, which is associated with first swelling and then destruction of myelin and eventually, of the axis-cylinders, followed by replacement with fibrous tissue. It is possible that certain central lesions of unknown etiology owe their origin to intermittent ischemia in relatively small circumscribed areas of capillary distribution.

A young woman under treatment for multiple sclerosis in November 1937 presented complaints and findings of peripheral vascular disorder in the lower limbs which revived previous speculation on the possibility of an ischemic basis of the central lesions of multiple sclerosis and led me to studies of the peripheral vessels in 18 cases of multiple sclerosis and in 2 cases of amyotrophic lateral sclerosis. In 10 of the cases of multiple sclerosis there was evidence of occlusion of the peripheral arteries; in 16 cases there was definite and in 2 cases suggestive evidence of abnormality of the capillaries of the nail beds, either as active spasm or as changes in structure and arrangement, and in 14 of 15 cases in which an occlusion index test (Landis and Gibbon) was applied there was an abnormal type of response. The curves obtained for both feet were either of the occlusive or of the spastic type, often differing in character on the two sides and showing in their form no consistent relationship to the age of the patient or the duration of the multiple sclerosis. In the 2 cases of amyotrophic lateral sclerosis there was no evidence of occlusion of the dorsalis pedis arteries; there was only moderate tortuosity and no spasm of the capillary loops of the nail beds, and the occlusion index test yielded normal curves.

This preliminary report is offered in support of a theory, not entirely new, that the lesions of multiple sclerosis develop, possibly in persons of "vasospastic diathesis," as a result of recurrent episodes of anoxemia in circumscribed patches of the central nervous system produced by occlusive ischemia, not on the venous but on the arterial side of the capillary beds. The pathogenesis of the sclerotic plaque might be presumed to be analogous to that of ischemic neuritis, the mechanism involving ischemia intermittently in the former and continuously in the latter, the final result being represented by proliferation of neuroglia in the former and by replacement with fibrous tissue in the latter. Further studies in pursuit of additional support for this hypothesis are in progress. It is recognized that the abnormal peripheral vascular findings may represent a result of central lesions which affect vasomotor outflow, but analysis of the cases studied does not favor this interpretation.

JAMES M. STANTON, M.D., *in the Chair*

Regular Meeting, April 20, 1939

PROBLEMS OF JUVENILE ABERRANT SEXUAL BEHAVIOR. DRS. R. W. WAGGONER and D. A. BOYD JR., Ann Arbor, Mich.

A study was made of 25 children who adopted aberrant sexual behavior as a regular and preferred method of sexual activity. It was attempted not to determine the basic cause of such aberrant practices, but rather to explore some of the social, emotional and environmental factors which were important in the development of the problem. An effort was made to understand the sexual behavior in the light of the total individual organism and the total situation rather than as an isolated part of the personality pattern.

The children presented individual problems, but there was a tendancy to certain groupings by virtue of common etiologic mechanisms. The first group included children whose home environment was characterized by parental overprotection and solicitude, with the consequent creation of a powerful, unwholesome parent-child relationship. In the second group were several children from homes of parental rejection. These children had personality patterns of immaturity, feelings of inferiority and inadequacy and sexual reactions on a childish level. In the third group were children whose perverse practices appeared to be related to defects in their personality organization. In some this disability was primarily an intellectual deficiency associated with powerful instinctive drives and weak inhibitory mechanisms. Others had physical handicaps, such as small stature, overgrowth, deformity or bizarre appearance, with consequent reactions of seclusive behavior and emotional immaturity.

Study of the 25 cases revealed that aberrant sexual practices in children stand in close relation to the more familiar types of juvenile behavior problems. In many cases the perverted sexual trends were so inextricably connected with the general personality and delinquency pattern that any effort to separate this particular behavior would be artificial and unwarranted. An attempt was made to evaluate the favorable and unfavorable factors which had reacted on the child. In the majority of cases it appeared that the home, church, school and community had failed to exert a practical and healthy influence in preventing the development of the problem. Of these factors, the failures and inadequacies of the home were most outstanding, and the defects in the personality structure of the children appeared to be closely associated with and a reflection of the unwholesome familial relationships.

ACUTE ASCENDING PARALYSIS, WITH A CLINICAL AND PATHOLOGIC REPORT OF CASES IN WHICH THERE WAS FATAL TERMINATION. DR. R. N. DE JONG, Ann Arbor, Mich.

The syndrome of acute ascending paralysis, or Landry's paralysis, may occur in association with a variety of infectious and toxic processes, and in many cases of poliomyelitis, transverse myelitis and myelomalacia the onset of the symptoms suggests ascending paralysis. No constant pathologic changes have been described in this condition, and many authors have expressed the belief that Landry's paralysis should be considered either as a form of poliomyelitis or as a variety of polyneuritis.

Pathologic examinations were made in 4 cases in which the clinical course followed closely that originally described by Landry. There was no evidence of inflammation, cellular infiltration, glial proliferation or degeneration of tracts within the spinal cord. The essential lesions were degeneration of the peripheral nerves and the anterior horn cells. In some cases the degeneration of the anterior horn cells consisted of pyknosis and shrinking and was considered primary, but

these changes were accompanied by alterations in the peripheral nerves. In other cases there were swelling, chromatolysis and vacuolation of the anterior horn cells, giving the so-called axonal type of degeneration, which is believed to be secondary to changes in the axis-cylinders. It can be assumed that the degenerative process is one that involves the motor nuclei or the peripheral nerves or both, and is therefore characterized by involvement of part or all of the final common pathway of the motor impulses. The etiologic factors in the process cannot be arrived at from this study, but the changes are essentially degenerative and may be considered resulting from an acute toxic process involving both the central and the peripheral nervous system. No evidence of infection was found in any case.

The term acute ascending paralysis probably should be employed in place of Landry's paralysis. It should be used, however, only to describe the mode of onset and progress of the condition, not to designate a specific nosologic or pathologic entity with a single cause. The term should be used only in cases in which the clinical syndrome is similar to that described by Landry and in which no definite etiologic factor, such as poliomyelitis or a specific infection or toxin, is suspected. In cases in which the cause is known but the syndrome is indistinguishable from acute ascending paralysis the condition may be referred to as Landry's syndrome.

NEUROLOGIC SYNDROMES ASSOCIATED WITH DEVELOPMENTAL ANOMALIES OF THE OCCIPUT, ATLAS AND AXIS. DR. C. F. LIST, Ann Arbor, Mich.

Systematic use of roentgenograms has revealed that congenital bony malformations of the occiput, atlas and axis are not rare. Such skeletal deformities frequently are associated with characteristic neurologic syndromes which may be produced in three ways: (1) by direct compression of the bone; (2) as an expression of an independent developmental anomaly of the central nervous system at the level of the lesion in the bone, or (3) by a combination of factors 1 and 2.

To understand the bony deformities, knowledge of the embryonic development is necessary. The following developmental anomalies, which per se do not cause neurologic signs, are not uncommon: (1) cervicalization of the occipital bone ("manifestation of an occipital vertebrae"); (2) occipitalization of the atlas, i. e., fusion of the atlas to the occiput ("assimilation of the atlas"); (3) spina bifida occulta posterior of the atlas, and (4) fusion of other cervical vertebrae.

Hypoplasia of the basiocciput leads to invagination of the upper cervical portion of the spine into the posterior cranial fossa, as the result of counterpressure of the cervical spine exerted against the base of the skull. The clivus becomes elevated, thus increasing the basal angle (platybasia). Severe degrees of this condition, in which the entire rim of the foramen magnum is mushroomed into the cranial cavity, have been termed "basilar impression."

If the atlas is fused to the occiput, the dens of the axis malformed or its ligaments malformed, anterior dislocation of the skull and atlas on the axis may occur. This dislocation may be mobile, when the ligaments of the dens are undeveloped. There are always more or less severe narrowing of the neural canal between the dens and the posterior rim of the foramen magnum and slight cranial displacement of the cervical portion of the spine. Patients with the deformities described hold their heads in a peculiar position. When several cervical vertebrae are fused the neck appears extremely short (Klippel-Feil's syndrome, *homme sans cou*).

The neurologic symptoms resulting from basilar impression (platybasia) consist of involvement of the lower cranial nerves (ninth to twelfth) with spastic hemiparesis or tetraparesis. Cerebellar signs are sometimes prominent; nystagmus is always present. Although internal hydrocephalus may develop, a marked syndrome of increased intracranial pressure rarely occurs.

In developmental dislocation of the atlas on the axis, the first or second cervical segment of the cord is compressed just below the foramen magnum. There

is a spastic ataxic syndrome with nystagmus in the less advanced forms. Erroneous diagnoses, such as multiple sclerosis, Friedreich's ataxia and cerebellar ataxia, are often made if the skeletal changes are overlooked. Advanced forms show severe spastic tetraparesis, with spinal automatisms and radicular involvement of the spinal accessory nerve. The sensory changes, which may be surprisingly slight, concern chiefly the qualities mediated by the posterior column. Lumbar punctures may reveal a partial manometric block.

Bony deformities of the occipitocervical region may be associated with developmental malformations of the hindbrain and cervical cord, e. g., with Arnold-Chiari's deformity. This anomaly consists of a tonguelike protrusion of maldeveloped cerebellar tissue into the spinal canal, with caudal displacement of the fourth ventricle and kinking of the spinomedullary junction. Arnold-Chiari's deformity produces clinically a vestibulocerebellar syndrome, with static ataxia and nystagmus. Since the malformation plugs the foramen magnum, obstructive hydrocephalus with signs of increased intracranial pressure develops; in fact, in some cases the typical picture of a midline cerebellar tumor is simulated. Spinal symptoms, especially those referable to a lesion of the posterior column, are slight. Other developmental anomalies of the nervous system (e. g., meningocele) are common in these cases. Lumbar puncture reveals a partial or complete block, and myelographic examination shows a characteristic filling defect corresponding to the spinal extension of cerebellar tissue. In the presence of increased intracranial pressure, lumbar puncture is contraindicated and ventriculographic examination advisable.

Malformations of the occipitocervical bones are sometimes combined with dysraphic disorders of the nervous system, such as hydromyelia, certain forms of syringomyelia and dysontogenetic ectodermal neoplasms of the cord (dermoid, ependymoma). In these cases pronounced sensory disturbances of a dissociated type with a segmental, high cervical distribution, may be present. The diagnosis is further aided by lumbar puncture and myelographic examination.

In treatment in these cases one must endeavor to accomplish two objectives, viz., the decompression and immobilization. The decompressive operation consists of combined suboccipital craniotomy and upper cervical laminectomy. While excellent results were obtained in cases of Arnold-Chiari's deformity, little improvement was accomplished in those of basilar impression and advanced altantoaxial dislocation. Fixation by implantation of bone grafts is indicated in cases of mobile dislocation.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

GILBERT HORRAX, M.D.

Regular Meeting, April 20, 1939

SUPERSTITIOUS SELF PROTECTION IN PSYCHOPATHOLOGIC CONDITIONS. DR. G. COLKET CANER.

Self protection may be stimulated by superstition and may be expressed in superstitious patterns. The superstition that unusual good fortune leads to misfortune is widespread and leads to a compulsive avoidance of unusual good fortune. This is of importance in puritanism, the resistance to getting well, excessive worry and pessimism. The superstition that misfortunes occur in groups is grounded in the belief of primitive man that misfortunes are caused by hostile gods or spirits. The idea that the powers that control fate may be moved to pity and mercy by suffering is still present in the unconscious of most persons. It has led to an unconscious mechanism of self protection through suffering. This mechanism may

be activated by life threats and by superstitition, and may continue to function autonomously once it has been activated. It is of importance in the psychopathologic reactions of everyday life, in neuroses and perhaps in depressions and other psychoses.

A superstitious belief in the "omnipotence of thought" is of practical importance in psychiatry and in general medicine.

The essential facts are given in 3 cases in which a threat precipitated symptoms which seemed to be the expression of unconscious self protection by suffering.

The development of attitudes which will offset too strong a reaction of unconscious self protection is one of the major tasks of psychotherapy.

DISCUSSION

DR. C. M. CAMPBELL: Dr. Caner's paper is stimulating; his formulations are ingenious. Conditions of depression are hard to interpret. It is difficult to feel that one is on sure ground in regard to interpretation. Some may see in the depression a masochistic reaction; others may hold the depression to be a compensatory reaction determined by a feeling of guilt. Dr. Caner has made the interesting suggestion that it may be the resurrection of a tribal outlook and mode of thought. The evaluation of this interpretation would require the understanding of beliefs in many cultures and the formulation of the central features which seem to be particularly related to fundamental human traits.

DR. I. H. CORIAT: Some one once said that blood runs like a red thread through Shakespeare's "Macbeth." The same thought might be applied to the occurrence of superstition in human culture. I do not think that it is necessary to postulate a racial unconscious in human beings (in the sense of Jung) in order to understand the various superstitions. The psychology of superstition can be best understood through a dynamic understanding of human wishes. Any person who feels an unconscious hostility, in the sense of illness or calamity, toward others is bound to be superstitious, in that he feels that the same calamity might occur to him because he is loaded with a sense of guilt. He is hoisted by his own petard.

Superstition occurs in all human beings, but if one wishes to find it in pure culture one must study the obsessive or compulsion neuroses. In the compulsion neurosis hostile wishes directed to others are most marked; therefore the superstition that something might happen to the patient himself becomes one of the symptoms of obsessional thinking.

I disagree with Dr. Caner that all compulsions are forms of magic; many of them are mechanisms for self punishment resulting from an unconscious sense of guilt. So far as mourning rites are concerned, I agree with Dr. Caner to a certain extent. On the other hand, one must remember that in certain primitive races, and also in the Irish wake, grief or mourning may assume the form of hilarity. It is an attempt to overcome and neutralize grief—a symptomatic group manic-depressive reaction. Superstition has been deeply rooted in the human psyche for thousands of years. Therefore I think that Dr. Caner's dynamic formulation is far too simple from either the interpretative or the clinical standpoint.

DR. IVES HENDRICK: I feel indebted to Dr. Caner for his scholarly presentation of anthropologic data, and I am in agreement with his generalizations. Whether or not superstitions are a race heritage of the unconscious mind, there can be no doubt that they occur in the life of every person of every culture, past and present. Whether one wishes to call this a "collective unconscious" is not important; the fact is indisputable. Whether a person inherits a specific content of superstitions is open to question, but the inheritance of the tendency to produce superstitions of one kind or another is beyond question.

I find the clinical portion of the paper less convincing. It is questionable whether the cure of the superstition is of much importance unless the emotional problems it solves for the patient are dealt with. Dr. Caner's first patient came

close to explaining the onset of his anxiety. He said: "I had the same thoughts about my dog that I have about my wife." The wife reacted to these remarks of her husband because actually they expressed his hostility toward her. She recognized that her husband had a fantasy that she would die. I want to ask Dr. Caner whether the antagonism between husband and wife was diminished by the treatment.

DR. G. COLKET CANER: In answer to the last question, I tried, but was unable, to elicit any hostility on the part of either the husband or the wife. They seemed to be devoted to each other. As I saw the patient only a few times, it is possible that some unconscious hostility may have been present. There is some between almost any man and wife. I think, however, that it was not great and that it would have been unwise to have brought it to consciousness. Even if one supposes that hostility between the husband and wife was of importance, the formulation which I am advancing still seems valid, for both fear and guilt lead to a reaction of self protection, and since no purposeful means of self protection would have been available it could find expression only in the superstitious pattern.

Whether or not the concept of the collective unconscious is valid does not seem of practical importance as far as the validity of this theory is concerned, since the pattern of superstitious self protection is developed by the conditionings of early childhood. As I have stated, each person learns in childhood that his parents are nicer to him when he is upset and suffering. The association between suffering and help and protection is so strongly established in childhood that it is easily reactivated later and leads to an attempt at self protection through suffering.

A ROENTGENOGRAPHIC SIGN IN CASES OF TUBEROUS SCLEROSIS OF THE BRAIN (MULTIPLE "BRAIN STONES"). DR. PAUL I. YAKOVLEV, Waverly, Mass., and DR. WILLIAM CORWIN, Waltham, Mass.

This paper appears in full in this issue of the ARCHIVES, page 1030.

SIMULTANEOUS RESPIRATORY AND ELECTROENCEPHALOGRAPHIC RECORDING IN CASES OF PETIT MAL. DR. STANLEY COBB, DR. WILLIAM W. SARGANT and DR. ROBERT S. SCHWAB.

Two interesting features of minor epileptic (petit mal) attacks are their frequent increase in states of emotional stress and their production by hyperventilation. In conditions such as hysteria it is well known that emotion may bring on hyperventilation. At the December 1938 meeting of this society (Studies on Respiration in the Psychoneuroses, ARCH. NEUROL. & PSYCHIAT. **41**:1071 [May] 1939), Finesinger demonstrated that even thinking of pleasant and unpleasant things may change the breathing patterns of neurotic subjects. Therefore, we set out to see if spontaneous alterations in breathing occur in cases of petit mal and if these changes are related to the number of seizures.

The technic used was to record the respiratory pattern and the minute respiratory volume by means of a basal metabolism machine while the patient was connected in the usual manner with the electroencephalographic apparatus. Records with the two sets of apparatus were carefully synchronized. Petit mal waves were measured in this investigation only if three or more abnormal waves occurred together. The subjects tested were outpatients taking phenobarbital or sodium diphenyl hydantoinate.

The first patient studied, a girl aged 13 with clinical petit mal attacks, showed striking irregularity in her breathing records. When the minute respiratory volume increased spontaneously, abnormal waves appeared in the electroencephalogram; they were absent during quiet breathing. For example, in a nine minute run with the average ventilation of 6.6 liters per minute no abnormal waves appeared. In contrast, during a similar run when the ventilation was 10.4 liters per minute five attacks, totaling one hundred and ninety-nine seconds, occurred.

In these charts it was found that many of the attacks of abnormal waves were preceded by short periods of spontaneous hyperventilation. In fact, it was possible on several occasions to anticipate an attack from a spontaneous increase in ventilation shown on the kymographic record of the basal metabolic rate before abnormal waves appeared in the electroencephalogram.

In another case of petit mal, that of a woman aged 21, the same relation existed between spontaneous increase in minute respiratory volume and the occurrence of abnormal waves in the electroencephalogram. This patient, in addition, showed a peculiar slowing of respiration during the actual attack, so that the record of her breathing had prominent gaps that coincided with each attack.

A third case, that of a boy aged 15, was found to be spontaneously hyperventilating on two occasions while connected with the basal metabolism machine. The electrical record was so irregular that measurement of the duration of each attack was difficult, and therefore Hoagland's delta index was used instead of measurement of the individual waves. The values obtained closely followed the changes in respiration, being high during the two periods of spontaneous hyperventilation and nearly normal when the patient was asked to breathe more quietly. When he was made to rebreathe carbon dioxide at an average consumption of 25 liters a minute the delta index also remained low.

In 3 other patients tested the correlation between minute respiratory volume and the amount of abnormal waves was not easily demonstrable. The differences between these two types of patients are now being investigated.

To make certain that our findings were of significance, our first patient was hospitalized for more intensive study. While an outpatient, taking sodium diphenyl hydantoinate, the correlation between hyperventilation and abnormal waves had been noted in five measured tests. When the patient was rebreathing carbon dioxide and hyperventilating, with a consumption of 30 liters per minute, no abnormal waves occurred, showing that hyperventilation per se was not responsible for the abnormal waves. When she was admitted to the hospital all drugs were withdrawn. Two days later she was tested with an air spirometer that was synchronized with the electroencephalographic apparatus in the same manner as the basal metabolism machine. The same correlation was found to be present when changes in breathing were induced instead of being allowed to occur spontaneously. There were more attacks when the subject was breathing normally than when asked to breathe slowly. Voluntary hyperventilation also increased the number considerably.

The patient was now given ammonium chloride, 150 grains (9.75 Gm.) daily, for four days and then reexamined. The correlation between changes in breathing and abnormal waves was found to have markedly lessened, and the attacks were greatly reduced in number. Sodum diphenyl hydantoinate, 4½ grains (0.292 Gm.) daily, was then added to the ammonium chloride. Three days later no abnormal waves were present, even with considerable hyperventilation, whereas in previous tests each drug alone had merely reduced the number of abnormal waves in the presence of spontaneous or induced hyperventilation. Our findings suggest, therefore, that, in addition to anticonvulsant therapy, the use of acidosis-producing drugs to counteract possible spontaneous hyperventilation in petit mal seems worthy of further investigation.

None of our conclusions are applicable to grand mal, since these phenomena have not been included in this study.

Conclusion.—It appears that in some cases of petit mal spontaneous changes in minute respiratory volume occur. This may alter the incidence of abnormal electroencephalographic waves by varying the carbon dioxide content of the blood.

DISCUSSION

DR. WILLIAM G. LENNOX: The striking influence of artificial changes in alveolar carbon dioxide on petit mal seizures (both clinical and electrical) has been known for years, but plotting a correlation between spontaneous changes in

respiration and electrical seizure patterns is a new contribution. As the authors indicate, such a relationship can be demonstrated in only a portion of the patients. The petit mal activity in a patient of mine could not be abolished by having her breathe high concentrations of carbon dioxide, but promptly disappeared when she opened her eyes.

If there are unusual spontaneous changes in breathing, the question arises whether there are also abnormal concentrations of carbon dioxide in the arterial blood. Brown-Séquard, in 1851, advanced the theory that epileptic seizures are brought on by the accumulation of carbon dioxide in the blood. Dr. and Mrs. Gibbs and I have taken arterial blood daily from a patient with much petit mal activity and have found that the degree of abnormality is greater on days when the arterial carbon dioxide is low. Furthermore, even when blood is taken without reference to individual seizures, patients subject to petit mal tend to show only lower, and those subject to grand mal only higher, values for carbon dioxide than normal persons used as controls. Finally, epileptic patients show a much wider scattering of carbon dioxide values than persons who are not subject to seizures.

The authors imply that their patients breathed more deeply because they were emotionally disturbed. Some patients have apnea during petit mal attacks, and it might be argued that disturbances of breathing whenever seen are only the outward expression of disturbed electrical rhythms in the region of the respiratory center.

Dr. William Sargant: I wish to thank Dr. Lennox for his remarks. It must be emphasized that in only a percentage of cases of petit mal are attacks brought on by hyperventilation. There are many other precipitating causes. It is impossible to say in what proportion of cases the phenomena described tonight are shown. That is a matter for future investigation. Probably it will not comprise a very large group of all cases of petit mal.

The synchronized method of recording respirations and brain waves that we have described may provide another means of assessing accurately the results of various drug therapies. I have been impressed with the fact that a patient after treatment may give the appearance of being well clinically, but when tested by the synchronized recording will still show abnormal brain activity. This method can be used to check the effects of treatment in the presence of known degrees of hyperventilation, with a view to obtaining a clear record of brain waves.

Dr. Stanley Cobb: I am not sure that we have answered the specific question Dr. Lennox asked. I think he asked whether we know how often spontaneous hyperventilation comes on before petit mal. We know only that it has happened in 6 cases. After looking at Dr. Lennox's records and our own, we realize that there are many cases in which there is not such a relation. In our records we have evidences that there is hyperventilation before there is any abnormality in the brain waves. That the abnormal nerve impulses act as the precipitant of the hyperventilation is not shown in the records of the brain waves.

I wish to add that this investigation was carefully carried through on only 6 patients. There must be many similar cases. It is of interest that hyperventilation, which we have used as an artificial method for eleven years, is now shown to appear spontaneously in a state of nature, so to speak.

Dr. Robert S. Schwab: It is difficult to measure hyperventilation accurately from inspection of a chart registering the respiratory rate. We found that it is necessary to measure exactly the minute respiratory volume in terms of liters per minute, which can be done from our records of the basal metabolic rate or from the air spirometer readings. Large changes in the minute respiratory volume can occur even when the rate is unchanged. I may point out, since we have discussed only 3 of our patients this evening, that we examined 22 patients, making a total of 80 observations with this method. We selected 6 of these patients for special study of spontaneous changes in ventilation.

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND THE NEW YORK NEUROLOGICAL SOCIETY

MORRIS GROSSMAN, M.D., *Chairman of the Section of Neurology and Psychiatry, Presiding*

Joint Meeting, May 2, 1939

TREATMENT OF ULCERATIVE COLITIS ASSOCIATED WITH HYSTERICAL DEPRESSION: REPORT OF A CASE. DR. GEORGE E. DANIELS (by invitation).

The case presented was that of a Jewish housewife aged 32 who had had three previous attacks of ulcerative colitis and was suffering from her fourth attack, which had lasted for nearly five years. In all four attacks emotional conditioning played an important role. Between the third and the fourth attack she had a miscarriage, at the beginning of the ninth month. The fetus was expelled into the toilet without her being aware that she was in labor. Only later, under psychotherapeutic treatment, did she recall significant circumstances and recognize the unconsciously motivated rejection. The miscarriage was followed by depression.

Six months later she again became pregnant. Her first pains precipitated severe tachycardia, the repetition of which subsequently introduced interesting conversion symptoms. She had an extended period of amnesia associated with this labor. Her fourth attack of ulcerative colitis began two weeks after delivery of a living child. While in the Presbyterian Hospital for treatment for the colitis, psychotherapy was begun. Antagonism toward her husband and child was evident, and marked dependence on her mother was significant.

After five months in the hospital, where she received various courses of medical treatment, she was discharged as improved. An impending relapse a few weeks after discharge led to intensive psychotherapy, with modified free association on the couch over a period of three and a half months. Through this she became conscious of her repressed hostility toward her mother. This she worked through sufficiently to free herself from the mother's domination and to reestablish her own home, without which she had little chance of making substantial imrovement. The social service department gave material aid in her reestablishment. Her first attack of asthma developed at this time, and there was a brief, severe return of palpitation and diarrhea.

Although from time to time she continues to have returns of palpitation and diarrhea, these are usually associated with definite conflict situations which, becoming aware of instead of repressing them, she is able to handle, and the danger of prolonged recurrence has been reduced. The colon, however, shows degenerative changes which may necessitate eventual colectomy. In view of the depressive picture with suicidal trends, however, surgical intervention is to be avoided if possible. These suicidal trends are not uncommon in patients with ulcerative colitis and are usually unconscious.

DISCUSSION

DR. C. P. OBERNDORF: In his vivid and clear presentation Dr. Daniels has reported a case in which the patient was observed over an extended period—a situation sometimes not true in psychoanalytic presentations. In Dr. Daniels' patient the symptoms began at 18 and persisted to the age of 32, during which time she had three attacks. A pregnancy occurred between the third and the fourth attack. During that time the patient presented a multiplicity of symptoms; in addition to the frequent stools, there were tachycardia, substernal pain and anal fistulas, with an extraordinary amount of attention and depression, and finally asthma and hay fever—quite a list of symptoms, or what one might call disease pictures. The close association between the premature delivery and the patient's hostility to her

mother seems evident. Another apparent feature is the increase in the patient's anxiety when the frequency of the stools decreased, but the entire picture is attributed to the hostility to a mother identification and an ambivalent attitude toward a deceased brother.

I can parallel this case with one which I have observed at Mount Sinai Hospital for about four years, in which the patient was practically exsanguinated through loss of blood from mucous colitis at the time the psychiatrist was called. The patient's illness primarily was dependent on incest with her brother at the age of 13. She was an Italian Catholic girl aged 24, and had had two previous periods of hospitalization. Because of the incest with her brother there developed subsequent hostility to him, but the hostility, in turn, represented an unconscious attachment. The hostility in her case was displaced toward the church, with the rejection of Catholicism, and subsequently toward society at large. On the basis of a psychocathartic approach the patient made marked improvement, gained in weight and was able to leave the hospital; here, again, the fundamental difficulty was not the colitis but deeper emotional conflicts. As a confusing circumstance there subsequently developed obstinate constipation. Then she became afflicted with disturbances of the upper gastrointestinal tract and vomiting. Finally there came a marked depression, with real thoughts of suicide. After partial rehabilitation, as in Dr. Daniels' case, through cooperation of the social service department we were able to place this patient in a training school for babies' nurses, where she made a good adjustment. Then something occurred which revived the symptoms of mucous colitis. A fortune teller mentioned to her an Egyptian marriage, which was associated in her mind with incest. The mucous colitis was sufficiently severe to necessitate her return to the hospital. At present she is doing well, but the idea of incest subsequently was shown to be directed not primarily toward the brother but also toward the father, at a much earlier age. The patient's symptom complex is still unresolved. The hostilities to the mother and the brother are outstanding psychologic factors; Dr. Daniels reports that his patient acquired asthma and hay fever. I have analyzed a case of asthma in which the psychologic mechanisms were almost exactly the same as those reported in cases of colitis. One comes, therefore, to an interesting question of organ involvement in persons with repressed hostility, namely, the choice of the organs affected. So far as I can see, any organ system having the three functions of intake, retention and expulsion can bear the burden of such a conflict, whether it be the lungs, the gastrointestinal system or the genitourinary system. At one time, Dr. Franz Alexander attempted to differentiate the functions of the upper and the lower gastrointestinal tract, maintaining that when the upper gastrointesinal tract was affected it was in a person who had repressed his desire to receive; when the lower portion was involved, it was in a person with repression of the tendencies to give. I do not believe that that is valid. A conflict based on repressed hostility might attack any organ system, wandering from one to another, as in the cases reported. What decides the organ chosen is still a mystery. There is good reason to suspect that the choice of a specific organ may be due to identification with another person (parent) or to an organ defect, and the organ chosen is the most vulnerable one in the body.

The final point is that of treatment. In hospital wards these patients are subject to all the influences of the medical atmosphere and mechanical appliances. It seems best to remove them from the hospital as soon as possible and to continue treatment in the outpatient department. There, some form of psychoanalytic treatment, such as Dr. Daniels has so successfully applied, can be carried out with great benefit to the patient; such an approach not only often relieves the patient of symptoms but also puts him in better position to handle himself in relation to his environment and internal problems. From an economic standpoint it is much cheaper than treatment in the hospital, with transfusions, expensive drugs and the cost of hospitalization.

Dr. C. A. V. Burt (by invitation): I have cooperated with Dr. Daniels and Dr. C. L. Janssen in the management of this extremely interesting and difficult patient. The progress of the patient bears abundant testimony to the value of psychotherapy in the treatment of ulcerative colitis. One of the most important considerations in the management of these patients is for the surgeon or internist to remember that he is dealing with a person as a whole rather than simply with a diseased colon. Aside from the extremely important psychotherapy, the treatment of nonsyphilitic ulcerative colitis, before it has reached the late, intractable form, is along conservative lines. (1) Foci of infection are eliminated. (2) A low residue, high protein and high caloric diet is given, and milk is eliminated, as it is not tolerated well. Elimination diets, by trial and error, are best. Skin sensitization tests are of little or no value. (3) Vitamin concentrates usually should be added to the diet: vitamin B complex, 1 to 10 mg. per day; ascorbic acid, 200 to 300 mg. per day, and cod liver oil (vitamins A and D), 1 ounce (29 cc.) per day. (4) Sedatives are employed for rest and relaxation. Tincture of belladonna, 10 to 15 minims (0.6 to 0.9 cc.), every four hours, may be given. (5) Anemia is treated by transfusions. Transfusions of irradiated blood are of little or no value; liver extract, 3 cc. once or twice a day, by hypodermic injection is preferred. (6) Autogenous vaccines in my hands have been of considerable value. (7) Local instillations or irrigations through the rectum or ostium have been disappointing; zinc peroxide has been most beneficial, but its effect has not been encouraging. (8) Sulfanilamide has not been tolerated well. Neoprontosil (the disodium salt of 4-sulfamidophenyl-2″-azo-7′-acetylamino-1′-hydroxynaphthalene-3′, 6′-disulfonic acid), 40 Gm. per day, has been administered to several patients in the Vanderbilt Clinic, with rather encouraging results, but it has not been used long enough to permit any conclusions.

The introduction of psychotherapy and the institution of local and general measures, as outlined, will result in remissions in a majority of cases. However, many patients come under care after they have reached the advanced, intractable stage of chronic ulcerative colitis. In this group extirpation of the diseased bowel is indicated. With failure of the conservative regimen, progression of the lesions, as seen proctoscopically, and advance of fibrosis of the colon, as observed roentgenologically, particularly in the presence of pseudopolypoid degeneration of the mucosa, one is justified in considering removal of the diseased colon. Dr. A. O. Whipple, of Presbyerian Hospital; Dr. H. W. Cave, of Roosevelt Hospital; Drs. R. B. Cattell and F. H. Lahey, of Boston, and many other surgeons have performed complete colectomy on many such patients, with gratifying results. Appendicostomy, cecostomy and colostomy have no place in the management of the intractable form of ulcerative colitis. Ileostomy as a curative procedure has been discarded. It diverts the fecal stream and temporarily reduces the toxemia, but the disease persists until the affected colon has been extirpated. Colostomy, on the other hand, when the lower portion of the sigmoid flexure and the rectum are involved, provides more comfort than an ileostomy, for the intestinal discharges through the colostomy opening are less irritating and are apt to be more solid. Ileosigmoidostomy is of limited value because of the danger that in the remaining colon and rectum the disease will develop later.

The general management of chronic ulcerative colitis has been, as a whole, difficult and disappointing. Cooperation of the psychiatrist with the surgeon and internist in the direction of treatment of patients in the earlier phase of the disease, before it has reached the intractable stage, should result in a much higher percentage of cures than has been possible under the old, individual form of treatment.

Dr. George E. Daniels: I owe an apology to Dr. Oberndorf for omitting the part in my paper concerned with asthma, but it was necessary to cut it down at the last moment. I may mention that hay fever and asthma appeared in my patient for the first time during the summer after she returned from the beach to New York to live alone with her husband and child; this is interesting in view of the fact that Alexander, in Chicago, and the group there believe that an asthmatic attack often represents the reaction to separation from the mother and

the inability to tolerate that separation. In a case of my own, one of asthma and hay fever, in which the patient is undergoing psychoanalysis, the connection of this particular reaction with the working through of such a conflict has also been demonstrated.

PSYCHOANALYTIC CONCEPTION AND TREATMENT OF THE NEUROSES. DR. SANDOR RADO (by invitation).

The somewhat capricious therapeutic results of psychoanalysis have forced revision of views on the pathology of the neuroses. This development was ushered in by Freud, who in 1926 reversed some of his earlier conceptions and recognized that the central role in the causation of neuroses is played by anxiety. Further insight was blocked, however, by the highly speculative hypothesis of instincts, so vague and remote as to be of questionable value in the interpretation of clinical observations. It was attempted, therefore, to segregate the factual findings of psychoanalysis from its metaphysiscal elements, and to describe the actually observable dynamics of the mind in terms of integrative ego (i. e., personality) function. According to this new frame of reference, which has been termed "egology," neuroses are considered as disturbances in integrative ego functioning and described in terms of a pathologic change in the ego (i. e., personality). Of the various integrative ego functions, only one is briefly discussed here, the disturbance of which is chiefly responsible for the disorders observed in neuroses. This is the safety function of the ego; I have called it emergency control. This control is integrated on three hierarchic levels. Its devices are: on the intellectual level, fear (apprehension); on the subintellectual or affectomotor level, the affect of anxiety, and on the subaffect level, pain. These devices drive the ego to emergency moves, emergency fortifications and reparative adjustments. In normal development of childhood the anxiety reflex, pertaining to the affectomotor level, is transformed into and superseded by the intellectual fear reflex. If this development is hampered and the anxiety reflex is allowed to persist morbid consequences follow, detailed study of which has given rise to the following concept: Neurosis is ordinary ego functioning altered by faulty measures of emergency control. In the pathogenesis of neurosis the first observable event is a disturbance in the development of the fear reflex, resulting in the survival of the anxiety reflex and the expansion of its affect manifestations into attacks; in the effort to control anxiety attacks the ego generates morbid fears, and is then pushed by these into faulty emergency measures, which invade and upset any or all of its functions.

The most important measures of pain control, of tremendous significance for the neuroses, are the manifestations of what I have termed the riddance principle. They are the physiologic riddance reflexes and the primitive riddance impulses. Neurotic fantasies are also considered as reparative adjustments acting vicariously for the disturbed function. In conclusion, I point to the correct method of utilizing these fantasies in the therapeutic procedure, together with the other symptoms derived from the reparative efforts of the neurotic ego to open up inferior sources of pleasure and profit as a compensation.

DISCUSSION

DR. GEORGE E. DANIELS: Dr. Rado is modest, and unless one had some historical perspective one might not fully realize that the developments presented represent largely his own contribution. What Dr. Rado has done, and by so doing has helped others to do, is to insist that in the psychoanalytic treatment of the neurosis one proceed from what one knows, without using speculations, interesting as they may be, as the directing plan. This has been motivated by a second goal, which for a long time the analyst hardly dared admit—the conscious desire to help or cure the patient. It was not that the analyst was less humane or less socially minded than other physicians, but that, just as Rado at present advises proceeding without too great reliance on the theory of instincts, Freud, to avoid certain errors and to encourage increase of badly needed knowledge, pointed out

that the patient often exploits the analyst's desire to make him well, and that knowledge can be gained and the danger of an impasse often avoided by concentrating on the investigative aspect of the procedure. This led to the idea that the analyst should not be interested in cure, but should only analyze.

Now, with the present accumulation of experience and knowledge, it is not necessary to deal with every patient as a subject of original and exhaustive research. One can more quickly make use of the material gained from the study of the individual case for purposes of treatment and begin to apply it from the first. This, as Dr. Rado pointed out, does not materially shorten the time needed for treatment, which seems to be dictated by the length of time necessary to make sweeping changes in personality.

Dr. Rado's approach, however, does give maximum time for the working through and reeducation process, making it possible more thoroughly to ground this process instead of leaving it to the chance that the investigative process alone will suffice. This increases the likelihood of success, especially in the more difficult cases, in which the analyst is asked to help in increasing numbers.

To simplify a theory that has tended to become complicated, Rado attempts to formulate the whole problem in terms of the ego. This is in line with his principle of utilizing what is known most about and proceeding from this point, as has been mentioned. Though the changes advocated by Rado do not cut down the total time of treatment, I believe that they do afford a valuable means of adapting psychoanalytic principles to general psychotherapy, which is so much in need of clarification. By dealing with the total treatment situation from the first and by progressing from the grosser to the finer psychopathologic manifestations, one accustoms oneself to work up to the therapeutic possibilities within the limits afforded.

I found Rado's reformulation of the theory of anxiety interesting and useful. I still think that this does not provide an explanation of why the neurotic person exploits suffering and pain to the degree that he does. That pain is the more fundamental and primitive is probable, but one is entering here, I believe, on the field of speculation. Dr. Rado does not have sufficient time to give the supporting data. I wish he could give further illustrations.

Though I agree with Dr. Rado that one should fall back on biologic knowledge rather than on biologic speculations, I believe one should be much more active than this, and help the biologist in the formulation of problems into which the analyst has gained insight empirically. In exchange for this, the biologist can aid us in clearing away vestiges of outworn theories of instincts. I agree that one should catch up with the facts, and for that reason it may be well to suspend use of unproved theories. It would be unfortunate, however, if one allowed the "riddance reflex" to go into action prematurely before one is sure what to amputate. The analyst has also to watch that an earlier caution to avoid unproductive biologic speculation does not close the door to his appreciation of the present great advance in biologic science and thus retard the very process which all agree is necessary: the separation of the wheat from the chaff of knowledge.

Dr. David M. Levy: Dr. Rado has offered a new conception of the defensive measures used by the personality in guarding against anxieties. On this theory I shall not comment, except to utilize it as evidence of general trends in the development of psychoanalysis in the past decade in this country. In doing so, I am trying simply to portray my own feeling of the changes in emphasis and in points of view that I have seen in that period. These trends may not affect the analytic pursuit of any particular member of the profession, but may represent distinct influences that more or less pervade the field.

There has been, first, a reaction against authoritarianism in psychoanalysis. The argument that a thing is so because it has been so stated in the writings of Freud is heard less and less. Such an argument was fortified not by marshaling of data but by tying it to a theory already pronounced by Freud, even when that theory may have been his tentative formulation. There has been less stress on

purely corroborative research—the "Freud was right" type. Also, less has been seen of the fantastic in the speculations of psychoanalysts, the "skyscraper" theories built up by the magic of free association, with little regard for clinical data. A number of bold investigators in the field are responsible for a more pentrating psychoanalysis. Certainly, Dr. Rado has been a leading spirit among those who constantly propose the question: "On what facts is this inference based? What are the findings?" The same questions have been used to force definitions out of the class of vague categories, so that when words cannot be accurately defined they can at least be made to represent definite clinical symptoms. The stage of obeisance to Freud, of testing the value of a theory in terms of its agreement or disagreement with the master—a stage that has tended to hold back progress in the field—is giving way to a freer utilization of his doctrines, to taking for granted his historical importance as the founder and liberating the investigator from blind adherence to dogma.

This leads to a consideration of the psychosomatic investigations in which the Chicago Institute of Psychoanalysis, under Dr. Frank Alexander, has played a leading part. Such studies have required precise physiologic measurements during the course of an analytic procedure; for example, the influence of emotional difficulties on secretion of gastric juice and hypertension and, conversely, the influence of the sexual cycle on dream formation and on the attitude of the patient toward the analyst. All these studies introduce a highly empiric method into psychoanalytic investigation. They sound a new note. They represent also the type of data that other scientists can understand in terms of conventional scientific thinking. The argument used with the unanalyzed scientist that he cannot understand because he has not been psychoanalyzed does not apply to these investigative procedures; hence psychoanalysis is aided thereby in its freedom from scientific isolation Various studies on the control situations in children may be mentioned at this point. In these experiments, a typical situation out of which emotional difficulties arise in the child is produced in a standardized way. The child's handling of the situation thereafter is not hampered. These studies have produced definite and comparable investigations which add considerable data bearing on the problems of anxiety, hostility and sexual impulses in early childhood. Control studies are also made in this way. They thereby solve the necessary problem of controls, for which the prolonged analysis in the early years is hardly feasible.

There has been a series of contributions related to social and cultural factors. Dr. Abraham Kardiner, in the New York Psychoanalytic Society, has worked with a number of anthropologists, thereby insuring for psychoanalytic investigation more expert source material. Emphasis on the social and cultural phase of the psychoanalytic investigation is exemplified especially by Dr. Karen Horney's work. The importance of evaluating the so-called external factors in the analytic situation is obvious. When such emphasis goes to an extreme there develops a type of antibiologic psychoanalyst, with definite limitations in the interpretation of emotional life.

In regard to practical problems in therapy, one may note less reliance on premature interpretative cleverness and increasing skill in grasping general dynamics. There has grown a greater respect for the importance of symptom formations as protective devices of the patient that are of necessity rebellious to therapeutic modification. There is also a greater understanding of the limitations of psychoanalysis, hence an improvement in the selection of patients for this treatment. The Rorschach test has played an important role in this regard. Through its use, the term "psychoanalyzability" is appreciated. It is a remarkably important contribution of a psychoanalyst to testing devices. Through responses to the ten standardized ink spots, the important criteria for psychoanalyzability can be deduced. These have to do with personality rigidities, ability to form concepts and enter into free associations, pathology of thought processes, impulsivity and acting-out tendencies.

It is not my purpose to describe in any thoroughgoing manner the contributions made in psychoanalytic research. I have utilized a sufficient number of observa-

tions to indicate, I hope, that psychoanalysts have not been rigidly formulated in their thinking, that they show evidence of a healthy growth in their scientific pursuits.

PSYCHIATRIC STUDY OF A MIRACULOUS "CURE" AT LOURDES. DR. SMILEY BLANTON (by invitation).

Louise Jamain came to Lourdes, France, after having been ill for about ten years and after having had fifteen abdominal operations and pleurisy with effusion; she had been proved to have tuberculosis of the lungs and intestines by a bacteriologic study one month before she came to Lourdes, on March 29, 1937. Lourdes is dedicated to the Holy Virgin, who appeared as an apparition to Bernadette Soubirous in February 1858. The patient had been unable to eat solid food since January 22 (about three months before she came to Lourdes). She also had hemorrhages from the lungs and a temperature of from 39 to 39.5 C. (102 to 103.1 F.).

After receiving the blessing in the procession she slept well; her temperature fell, and she began to eat well. Two days later she went to the medical bureau, where it was found that she had no signs of active illness. She returned to the hospital in Paris and stayed there for ten days; bacteriologic examination gave negative results. The patient took a position in Paris on May 10 and has been working steadily since.

The interesting point is that there was no convalescence whatever and that the patient seemed to be very ill when she came to Lourdes. There seems to be no reason to doubt the honesty of the medical records or of the physicians who made the examinations before she came to Lourdes and after she returned.

As explanation of the cure, coincidence, suggestion and transference are suggested.

DISCUSSION

DR. A. A. BRILL: Dr. Blanton has told of something that is not at all theoretic, not at all complicated. What he wants to have explained is how Mlle. Jamain happens to be alive and seemingly cured after she had undergone so many physical trials, after it was definitely diagnosed that she was suffering from tuberculosis. She was evidently cured through a pilgrimage to Lourdes. In his endeavor to explain this miracle, Dr. Blanton is unprogressive enough, in the light of the last discusser, to quote Freud. That I think is terrible!

Five years ago I read a paper before this assembly (Psychic Suicide, ARCH. NEUROL. & PSYCHIAT. **32**:880 [Oct.] 1934), in which I went the other way and showed that people can die "on purpose." They do not wish to live and they die. I have collected many cases since, and have taken material both from biology, and, strange to say, from sociology to corroborate the fact that some persons, notably of primitive races, can even die at will when they so desire.

I shall cite a case. In this case the person happens to be myself. I am willing to sacrifice myself on the altar of science before you. When I was 20 years old I suddenly had an attack of hemoptysis, which recurred a few times. I consulted a friend, a medical student at the College of Physicians and Surgeons. He took me to Dr. G., his prosector, who examined me and indirectly told me that I had little time to live. My friend, the medical student, then took me to the Vanderbilt Clinic, where I was examined by Dr. Norrie and was told that I had a small cavity, but that I would recover. I did not become hysterical or upset over it, probably because I did not appreciate its significance. Please remember that I was just beginning my sophomore year in college. However, I did not care to die, and somehow I lived on. As time went on, I began to doubt whether I ever had tuberculosis, but when I was examined for the Army in 1918 and was roentgenographed it was found I had a healed cavity. I saw it plainly. How, I should like to ask Dr. Blanton, did I get well? I never went to Lourdes, or to any place resembling it. Cases like the one he describes are numerous and

have been always a source of mystery. That somatic manifestations can appear and as mysteriously disappear is well known in religious and secular circles.

There was the case of Louise Lateau, who was examined by the famous Virchow; he said that in such cases all one can say is that it is either a miracle or a deception; as he did not believe in miracles the presumption was that it was just trickery, deception. One cannot say that nowadays. There is the case of Theresa Neumann, of Konnersreuth, who has organic manifestations in the form of stigmas which appear regularly every Friday. She was repeatedly examined by able neurologists, of whom I need mention only one, Hoche, who wrote a little pamphlet on the subject (Die Wunder der Therese Neumann von Konnersreuth, Munich, J. F. Lehmanns Verlag, 1933). He did not pronounce these manifestations deceptions, but endeavored to explain them on neurologic and psychiatric grounds. Jürgensen (Okkulte Hautblutungen, *Deutsches Arch. f. klin. Med.* **176**:550 [July] 1934) actually gave the physiologic mechanism of occult hemorrhages of the skin. Such cases, I agree with Dr. Blanton, are explainable on the basis of identification, which he calls in his case transference. Such cases and manifestations are of common occurrence. All have seen patients with mucous colitis and gastric ulcers who have recovered, some after they were almost moribund. I have seen and reported such cases. How the principle works I do not know, and it will be a long time before one will find out. There is no question that such cases exist. I do not think that they are all deception. I believe there is more force in the individual patient as far as his instincts for life and death are concerned than one discerns with present knowledge.

Dr. Carl Binger (by invitation): One must assume that the data which Dr. Blanton presented are facts. If they are not facts there is no use in discussing them. In any case, one cannot establish the truth of them by discussion. Assume that these observations have been made and that they are factual. It is probably true that this young woman, Mlle. Jamain, suffered from a hematogenous tuberculous infection. One might guess that there was involvement at the root of the lung or in the hilus, and that an infected lymph node disseminated bacteria in the body, producing lesions in the pleura, the lung, the peritoneum and various abdominal viscera. In this type of tuberculosis—I do not speak as an expert—spontaneous remissions do occur and are sometimes mistaken for cures. It is possible that this young woman had a spontaneous remission and that at some future time she may have another active tuberculous infection. However, the remarkable fact, and I shall assume it is a fact, is that the remission occurred in such an extraordinarily short time. Therein lies the miracle—that this person, sick one hour, was apparently well the next. In Dr. Blanton's case histories, the most significant fact about them is that these patients had all been to a great many physicians. I counted that some of them had seen twenty or thirty physicians before going to Lourdes. I suspect that this is part of the preparation for cure, and the miracle occurs when finally the Good Mother takes care of these long-suffering patients. To be sure, to call this the result of transference is not an explanation. Transference is itself a miracle into which there is as yet little insight. However, it is perhaps preparatory to a deeper understanding.

It seems to me that an inquiry of this sort is wholly justified scientifically. One should take a cue from William James, to whom nothing human was alien; certainly, nothing human should be alien to the province of science. An old teacher of mine, Professor Abel, of Johns Hopkins University, gradually developed in his talks with his students a kind of *religio scientifici*, of which there were three chief tenets. One was that in undertaking a piece of scientific research one should have a clearcut *Fragestellung*, in other words, a well defined problem. Dr. Blanton has this. To try to explain the psychodynamics of miraculous cures is a thoroughly reasonable scientific venture. The second tenet was that if in the course of one's research one needed to study Sanskrit to help tackle the problem, one should study Sanskrit. Dr. Blanton has explored deeply the medieval history of the Catholic Church. The third tenet was that, unlike the Red Queen in "Alice

in Wonderland," a good scientist must be ready to believe six impossible things before breakfast. Apparently, after dinner at least, Dr. Blanton is able to.

DR. SMITH ELY JELLIFFE: I, undoubtedly like many here, have been to Lourdes. In 1910 I spent a week there. My wife was with me. She was a competent French student and she made friends at Lourdes. She was invited to join with the ladies of France because, as you know, it is the Bourbon ladies of France who are foremost in the movement. She was invited to do exactly what those ladies did, and so for a week we entered deeply into the work. She was in the piscine, or bathing, grotto. The doctors, priests and others were further interested in me because I, forsooth, at that time was professor of psychiatry at Fordham University. Here was an American doctor, not a Catholic, professor at a Catholic university; this was certainly a phenomenon, so they were much interested in my attitude and point of view. I was much interested in them, and even more intrigued by the phenomena, because the thing is colossal. It is a magnificent panorama. One has only to read Zola's "Lourdes" and Huysmann's "Lourdes" to appreciate what the setting is.

Did I see cures? I saw hundreds of them, literally hundreds of them. But what were they? All know what they were: One after another, people came with paralyses and anesthesias, nauseas and vomitings and pareses, which ran the entire gamut of conversion phenomena. There were hundreds of persons with hysterias, and they were cured for the time being, just as one knows that throughout the ages such mass activities have relieved most hysterias.

There was a sad thing throughout the whole spectacle, for along with a number of the so-called hysterias I saw at least 50 to 60 cases of multiple sclerosis. I saw a lot of irreversible organic diseases. All diseases involve organs, and hence are organic. These were irreversible. Behavior had eaten itself into structure and could not be brought back. Cures took place; there is no doubt they did—tuberculosis and other conditions—just as one sees every day in medical practice. To call the process transference is not enough, but transference as a concept is on the way to an understanding of the curative process. What lies behind transference—whether the mother or the father or the whole situation—one cannot tell without minute detailed analysis of each and every sick person. To generalize on a verbal symbol of a disease is nonsense.

DR. SMILEY BLANTON: Dr. Jelliffe's studies in organic and functional disease are well known, and I am indebted to him for the helpful statement that everything is organic. The question is whether or not the organic change is reversible. I realize that the word transference is not a complete explanation of the cures at Lourdes, but at least it takes one a step farther and seems to be more specific than such vague terms as "suggestion," "environment" and "mass psychology."

I have been unable in this brief time to discuss the influence of the transference, the relation it bears to mother worship and the part it plays in the relation of the child to mother and father. I feel definitely that there is a force for healing at Lourdes and at many other places. For example, the same healing force occurs in the relationship between the physician and the patient. A friend of mine, a physician in a surgical hospital, in discussing these cures, said that he had had 2 patients with tuberculous fistula who suddenly recovered, and added rather facetiously: "I suppose the Blessed Virgin was here and cured these cases." I replied: "Perhaps she was, or some substitute for her." Cannot the physician be a substitute for a mother or a father? A naive, simple person could easily think of the physician as a godlike person, with his gown and his strange ceremonies in the operating room.

In closing, I may say that there is a definite force for healing which occurs in Lourdes and in similar places which has not yet been adequately evaluated by the medical profession.

Book Reviews

Frustration and Aggression. By John Dollard, Leonard W. Doob, Neal E. Miller, O. H. Mowrer and Robert R. Sears, in collaboration with Clellan S. Ford, Carl I. Hovland and Richard T. Sollenberger. Price, $2. Pp. 209. Publication of the Institute of Human Relations. New Haven, Conn.: Yale University Press, 1939.

This study takes as its point of departure the assumption that aggression is always a consequence of frustration. More specifically, the proposition is that the occurrence of aggressive behavior always presupposes the existence of frustration and, contrariwise, that the existence of frustration always leads to some form of aggression. It is the functional unity represented by the phenomena of catharsis and displacement that justifies attaching the label of aggression to the variety of responses considered in this theoretic presentation.

"Strikes and suicides, race prejudice and reformism, sibling jealousy and lynchings, satirical humor and criminality, street fights and the reading of detective stories, wife-beating and war" are brought under a sort of common denominator. The authors are indebted to the freudian psychology, wherein the dynamics of aggression and frustration have been deduced from clinical experiences. Their data, however, are derived from many and varied investigators. Adolescence, criminality, democracy, fascism, communism and the primitive Ashanti society are all fields for the understanding of aggression.

Those whose work is clinical will welcome the systematic and critical treatment because of a perspective not otherwise obtainable. The section on "Criminality" is one of the best; here, in clear and impartial style, the "variables" of crime are taken and evaluated.

Notices

CUMULATED INDEX OF THE ARCHIVES OF NEUROLOGY AND PSYCHIATRY

Requests have been received for a twenty year index of the ARCHIVES OF NEUROLOGY AND PSYCHIATRY. Before serious consideration is given to the production of a cumulated index, it is desirable to know whether the demand for it would be sufficient to warrant its sale at not to exceed $6 per copy; that is, whether one thousand copies could be sold. It will be appreciated if those who are interested in such an index will fill out and send the form which appears below to the Managing Editor at the publication office, 535 North Dearborn Street, Chicago.

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Abnormalities and Deformities: See under names of diseases, organs and regions, as Acromegaly; Corpus Callosum; Hydrocephalus; etc.
Abscess: See under names of organs and regions, i. e., Brain, abscess; etc.
Acetarsone, transitory spasmodic myopia caused by use of, 1170
Acetylcholine: See Choline and Choline Derivatives
Acid, Ascorbic: See Vitamins, C
  Cevitamic: See Vitamins, C
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